EXHIBIT A

Public Version

UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, DC

Before The Honorable Clark S. Cheney
Administrative Law Judge

In the Matter of CERTAIN PRE-FILLED SYRINGES FOR INTRAVITREAL INJECTION AND COMPONENTS THEREOF	Investigation No. 337-TA-1207

COMMISSION INVESTIGATIVE STAFF'S PRE-HEARING BRIEF

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CPreBr.	Complainant's Pre-Hearing Brief
CX	Complainant's Exhibit
CDX	Complainant's Demonstrative Exhibit
CPX	Complainant's Physical Exhibit
JX	Joint Exhibit
RPreBr.	Respondents' Pre-Hearing Brief
RX	Respondents' Exhibit
RDX	Respondents' Demonstrative Exhibit
RPX	Respondents' Physical Exhibit

I. INTRODUCTION

Pursuant to Ground Rule11.2, the Commission Investigative Staff ("Staff") hereby submits the following Pre-Hearing Brief. In summary, the Staff expects the evidence to show no violation of Section 337 by Respondent Regeneron Pharmaceuticals, Inc. ("Regeneron") because the asserted claims are invalid.[1]

In the event the Administrative Law Judge finds a violation, however, the Staff expects the evidence to support the issuance of a limited exclusion order and cease and desist order against Regeneron. The Staff further believes the evidence regarding the public interest will show that any Commission orders should be delayed for at least [redacted] to ensure an uninterrupted supply of the relevant anti-VEGF drugs.

A. Procedural History

The Complaint in this matter was filed on June 19, 2020. (EDIS Doc. ID 713042 ("Complaint").) The Complaint filed under Section 337 of the Tariff Act 1930, as amended, 19 U.S.C. § 1337, alleges infringement of certain claims of U.S. Patent No. 9,220,631 (JX-0001) ("the '631 patent") based on the importation into the United States, sale for importation into the United States, and sale within the United States after importation of certain pre-filled syringes ("PFS"). The Complaint named only Respondent Regeneron Pharmaceuticals, Inc. ("Regeneron"), and asserted claims 1–6 and 11–26 of the '631 patent. The notice of institution

[1] As explained below, the Staff believes the asserted patent is infringed by the accused products, and that Novartis has met the domestic industry requirement.

("NOI") was published in the Federal Register on July 27, 2020. *See* 85 Fed. Reg. 45227.

On August 4, 2020, the Administrative Law Judge ("ALJ") set a 16-month target date. (Order No. 6.) The target date is thus November 29, 2021, and a final initial determination on violation ("ID") is due on July 29, 2021. (*Id.*) The ALJ issued a procedural schedule on August 17, 2020, setting a *Markman* hearing for December 10, 2020, and trial from April 19-23, 2021. (Order No. 8.)

Regeneron filed a Response to the Complaint on August 25, 2020. (EDIS Doc. IDs 718105 (conf. vers.) & 718109 (public vers.) ("Response").)

On October 9, 2020, the parties filed a Joint Disclosure of Proposed Claim Constructions ("JCC"). (EDIS Doc. ID 721764.) On November 10, 2020, the private parties filed opening claim construction briefs. (EDIS Doc. ID 724600, Novartis's Opening Claim Construction Brief; EDIS Doc. ID 724594, Regeneron's Opening Claim Construction Brief.) The Staff filed a claim construction brief on November 17, 2020. (EDIS Doc ID 725440.) The only contested issues addressed by the parties' briefs related to indefiniteness under 35 U.S.C. § 112.[2] On November 24, 2020, the private parties filed responsive claim construction briefs. (EDIS Doc. ID 726358, Novartis's Responsive Claim Construction Brief; EDIS Doc ID 726359, Regeneron's Responsive Claim Construction Brief.) The ALJ conducted a *Markman* hearing on December 10, 2020. (EDIS Doc. ID 727758, *Markman* Hearing Tr.) The

[2] The parties put forward certain joint constructions, as noted below.

parties filed Post-Hearing *Markman* Briefs on December 21, 2020. (EDIS Doc. IDs 728667 (Novartis), 728674 (Regeneron), 728657 (Staff).)

On December 11, 2020, the ALJ granted the private parties' request to modify the procedural schedule by adjusting certain dates related to fact and expert discovery. (Order No. 20.) The amended schedule did not change the date for the hearing, ID due date, or target date. (*Id.*)

Fact discovery closed on December 18, 2020. (Order No. 20.)

On January 7, 2021, the ALJ denied Regeneron's request to terminate the investigation based on lack of standing. (Order No. 22.) The ALJ also denied Regeneron's request to amend the Response to add a standing defense. (Order No. 23.)

On February 18, 2021, the ALJ determined to grant Novartis's request to terminate the investigation as to claims 2, 14, 15, and 26. (Order No. 26.)

Also, on February 18, Novartis moved for summary determination on the issues of infringement, and the technical and economic prongs of domestic industry. (EDIS Doc. ID 734529 ("MSD").) Regeneron opposed the MSD only as to the economic prong of domestic industry. (EDIS Doc. ID 735497.) The Staff supported the MSD. (EDIS Doc. ID 735516.)

Expert discovery closed on February 22, 2021. (Order No. 20.)

On March 17, 2021, the ALJ determined to grant Novartis's request to terminate the investigation as to claims 18, 19, and 20.[3] (Order No. 29.) Claims 1, 3–6, 11–13, and 16, 17, and 21–25 of the '631 patent remain asserted in this investigation. (*Id.* at 2 n. 1.)

The private parties filed their respective pre-hearing briefs on March 12, 2021. (EDIS Doc. ID 736888, Novartis Pre-Hearing Brief ("CPreBr."); EDIS Doc. ID 736893, Regeneron's Pre-Hearing Brief ("RPreBr.").) Pursuant to Order No. 30, the private parties filed corrected briefs on March !!, 2021, which replaced CX and RX exhibit numbers with their equivalent JX numbers. (Order No. 30; EDIS Doc. IDs 737750 (Novartis) & 737762 (Regeneron).)

B. The Parties

1. Novartis

Complainant Novartis Pharma AG ("NPAG") is a Swiss company located in Basel, Switzerland. (Complaint, ¶ 10.) Complainants Novartis Pharmaceuticals Corporation ("NPC") and Novartis Technology LLC ("NT") are Delaware corporations located in East Hanover, New Jersey, 07936. (*Id.*, ¶¶ 11-12.)

2. Regeneron

Respondent Regeneron Pharmaceuticals, Inc. ("Regeneron") is a New York corporation located in Tarrytown, New York 10591. (Response, ¶ 16.) Regeneron sells in the U.S. the accused EYLEA PFS. (*Id.* at ¶ 17.)

[3] As of the filing of this brief, Order No. 29 is pending Commission review.

C. Overview of the Technology

The technology in this case involves terminally sterilized pre-filled siliconized syringes ("PFS") used for ophthalmic injection of a VEGF-antagonist drug.

1. VEGF-antagonists

VEGF, or vascular endothelial growth factor, is a "signal protein which stimulates angiogenesis."[4] ('631 patent, 6:32-33.) Over-production of VEGF in the eye is connected to a number of serious diseases that impact vision, including wet age-related macular degeneration ("wAMD"), diabetic retinopathy ("DR"), diabetic macular edema ("DME"), and macular edema following retinal vein occlusion ("MEfRVO"). (JX-0445, Dr. Szilard Kiss Opening Report, ¶ 11.) VEGF-antagonists are drugs that can be injected into the eye to block the action of VEGF and have been found to be effective in treating many of these conditions. (CX-0128; CX-0135.)

2. Pre-filled syringes

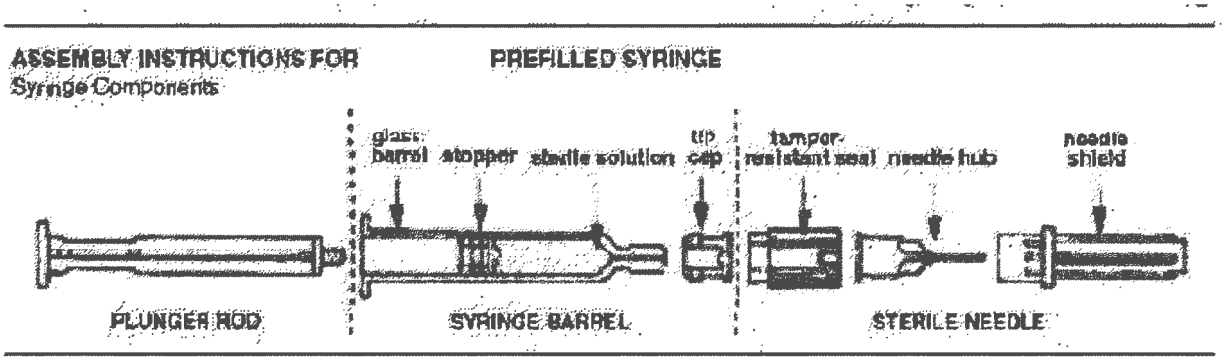
When a medicine is given to a patient in the vial presentation, the provider needs to use an empty syringe to draw out the correct dosage before injecting the patient. By contrast, a pre-filled syringe is a syringe that comes to the provider already filled with the correct dosage of medicine ready to use and inject. (JX-0434C, Opening Expert Report of Karl R. Leinsing, at ¶ 18; CX-0066.0007.)

Pre-filled syringe technology is quite old, having "debuted during World War II to accommodate the need for on the spot sterile medications in battlefield

[4] "Angiogenesis is the process by which new blood vessels form from existing vessel networks". (CX-1720.0001.)

hospitals." (RX-0475.0001.) "The next big push into the market came when Becton Dickinson and Company (BD, Franklin Lakes, NJ) began supplying glass prefillable syringes to support Dr Jonas Salks' poliomyelitis vaccination program in the early 1950s." (*Id.*)

Typical components of a pre-filled syringe include a plunger rod, a stopper, a syringe barrel, and a needle:



JX-0298, Shah 2009, at 2

3. Terminal sterilization

According to the '631 patent, "[i]t is important for patient safety and medicament integrity that the syringe and the contents of that syringe are sufficiently sterile to avoid infection, or other, risks for patients." ('631 patent, 1:15-21.) One way to sterilize a syringe is using terminal sterilization, "in which the assembled product, typically already in its associated packaging, is sterilised using heat or a sterilising gas." (*Id.*) Common sterilization methods such as heat or radiation are not appropriate for use with biologic drugs (such as the drugs at issue in this investigation). (CX-0598.0256; JX-0434C, ¶¶ 28-29.) The '631 patent discloses two known processes for terminal sterilization for use with the biologic

drugs used with the invention: ethylene oxide (EtO) or hydrogen peroxide (H_2O_2). ('631 patent, 9:49-52.)

4. Siliconization

The interior barrel of a pre-filled syringe is typically lubricated with silicone oil to ensure ease of use and consistency of the injection force. (CX-0188.0001, Chan 2012; '631 patent, 4:48-50.) With respect to ophthalmic injections, however, it is important to minimize the risk of silicone droplets being injected into the eye, as those droplets "can build up in the eye, causing potential adverse effects, including 'floaters' and an increase in intra-ocular pressure." ('631 patent, 4:50-55.)

Syringes can be siliconized using either "oily" siliconization or "baked-on" siliconization. (JX-0472.0003; JX-304.0003, 5; JX-0434C, ¶ 24.) In oily siliconization, the silicone oil is sprayed directly on to the interior of the syringe barrel. (JX-0472.0003; JX-304.0003, 5; JX-0318.0003.) In baked-on siliconization, an emulsion of silicone oil and water is sprayed onto the interior of the syringe barrel and then heated (*i.e.* "baked"); the water evaporates during the heating process and the silicone oil bonds with the surface of the glass thus reducing the amount of free silicone oil in the syringe. (*Id.*)

D. The '631 Patent

The '631 patent is titled "SYRINGE" and issued on December 29, 2015, from an application field on January 25, 2013. The named inventors are Juergen Sigg, Christophe Royer, Andrew Mark Bryant, Heinrich Martin Buettgen, and Marie Picci. (*Id.*) The '631 patent claims priority to several foreign applications, the

earliest of which are two European patent applications filed on July 30, 2012 (No. 12174860) and October 23, 2012 (12189649). (*Id.*) Novartis is claiming priority for the asserted claims only to the October 2012 application. (CPreBr. at 92 n. 55.)

The '631 patent has only a single independent claim, claim 1, which is directed to a "pre-filled, terminally sterilized syringe for intravitreal injection." ('631 patent, claim 1.) The syringe has a "nominal maximum fill volume" of 0.5 to 1 milliliters and contains a "VEGF-antagonist" with no more than "2 particles >50 μm in diameter per ml." (*Id.*) The syringe of claim 1 contains about 1 to 100 μg of silicone oil, while other dependent claims require 3-100 μg (claim 3) or 1-50 μg (claim 22).[5]

The '631 patent also asserts that a syringe must be "easy to use" in that "the force required to depress the plunger to administer the medicament must not be too high." ('631 patent, 1:37-40.) Further, siliconizing a syringe barrel "decreases the force required to move the stopper." (*Id.*, 4:50.) The '631 patent further explains that optimizing the force required to move the stopper, *i.e.* the "break loose force," is especially important when injecting medicine into the eye "where movement of the syringe during administration could cause local tissue damage." (*Id.*, 7:32-35.) Independent claim 1 of the '631 patent requires a break loose force of less than

[5] A microgram (μg) is one thousandth of a milligram (mg), *i.e.* 1 μg = 0.001 mg.

"about 11 N." Several dependent claims require a lower break loose force, and/or require a certain "stopper slide force."[6] (*Id.*, claims 14-16.)

E. The Products at Issue

1. Novartis's Domestic Industry Product

Novartis's domestic industry product is the PFS presentation of the drug brolucizumab, marketed under the name "BEOVU." (CX-0117C.0001.) BEOVU comes in two presentations for delivering the drug to a patient: a vial and a prefilled syringe ("PFS"). (*Id.*) The vial presentation has already been approved by the FDA and the PFS presentation is pending approval. (CX-0007.)

2. Accused Regeneron Product

The accused Regeneron product is the PFS presentation of the drug aflibercept, marketed under the name "EYLEA." (CX-0491C.) As with BEOVU, EYLEA is sold both in a vial and in a PFS. (*Id.*) Both versions have been approved by the FDA. (*Id.*)

F. Witness Testimony

The Staff does not presently intend to call any witnesses to testify at the evidentiary hearing but intends to present its case by way of exhibits and by examining the witnesses called by the other parties. The Staff may seek to call witnesses identified by other parties in their pre-hearing statements but who are then not called by the identifying party to testify at the evidentiary hearing.

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[6] The stopper "slide" or "glide" force is the force required to keep the plunger in motion. ('631 patent, 5:28-32.)

II. JURISDICTION

A. Subject Matter Jurisdiction

Section 337(a)(1)(B) declares unlawful, inter alia, "[t]he importation into the United States, the sale for importation, or the sale within the United States after importation by the owner, importer, or consignee, of articles that . . . infringe a valid and enforceable United States patent." 19 U.S.C. § 1337(a)(1)(B).

Novartis has properly filed a complaint alleging a violation of Section 337 as a result of the unauthorized importation into the United States, sale for importation into the United States, and/or sale within the United States after importation of certain pre-filled syringes for intravitreal injection and components thereof that infringe claims of the '631 patent. (Complaint, ¶¶ 1-9.) The Commission therefore has subject matter jurisdiction. *Amgen, Inc. v. Int'l Trade Comm'n*, 565 F.3d 846, 854 (Fed. Cir. 2009). Regeneron does not contest that subject matter jurisdiction exists. (RPreBr. at 56.)

Novartis is the assignee of the '631 patent, and therefore has standing to bring this investigation.[7] Regeneron does not contest that Novartis has standing.[8] (RPreBr. at 56.)

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[7] Specifically, through a series of assignments, it appears that Complainant Novartis Technology LLC is the assignee. (Complaint, Ex. 2, at pp. 29-33.)

[8] Regeneron's motion to terminate the investigation on standing grounds was denied by the ALJ, as was Regeneron's motion to amend the Response to add a defense related to the same standing argument. (Order Nos. 22 & 23.)

B. Personal Jurisdiction

Regeneron has appeared and participated in the investigation. The Commission, therefore, has personal jurisdiction over Regeneron. *See, e.g., Certain Windshield Wiper Devices and Components Thereof*, Inv. No. 337-TA-881, Initial Det. at 5 (May 8, 2014), *unreviewed in relevant part*.

Regeneron does not contest that personal jurisdiction exists. (RPreBr. at 56.)

C. In Rem Jurisdiction

The Commission has *in rem* jurisdiction when infringing articles are imported, sold for importation, or sold within the United States after importation by the owner, importer, or consignee. 19 U.S.C. § 1337(a)(1)(B). An exclusion order operates against goods, not parties, and therefore is not contingent upon a determination of personal jurisdiction over a foreign manufacturer. *See Sealed Air Corp. v. United States Int'l Trade Comm'n*, 645 F.2d 976, 985–86 (C.C.P.A. 1981)

Here, the Staff expects the evidence to show that the Commission has *in rem* jurisdiction over the products at issue. First, Regeneron admits that [redacted]. (EDIS Doc. ID 725222, Stipulation of Material Facts on Importation and Inventory, at ¶¶ 5-8; *id.* at Attachments 1-3 ([redacted])). Second, Regeneron does not contest that the EYLEA PFS, [redacted], infringes claims 1, 3-6, 11-13, 16, 17, and 20-23, and that claims 24-25 are infringed by physicians who administer EYLEA PFS. (RPreBr. at 59; EDIS Doc. ID 735497, Regeneron Response to Novartis MSD, at p. 18.) Regeneron also does

not contest that Regeneron indirectly infringes the asserted claims. (RPreBr. at 59; CPreBr. at 35-38.) Therefore, the EYLEA PFS is an article that infringes under Section 337, over which the Commission has *in rem* jurisdiction. *See Comcast Corp. v. Int'l Trade Comm'n*, 951 F.3d 1301, 1308 (Fed. Cir.).

The Respondents do not contest that *in rem* jurisdiction exists "over any of the Accused Components that have been imported into the U.S., as identified in Paragraph 7 of" CX-0778C. (RPreBr. at 56.)

III. LEGAL STANDARDS

A. Violation of Section 337

"The importation into the United States, the sale for importation, or the sale within the United States after importation...of articles that...infringe a valid and enforceable United States patent" constitutes a violation of Section 337. 19 U.S.C. § 1337(a)(1)(B).

B. Infringement

Under 35 U.S.C. § 271(a), direct infringement consists of making, using, offering to sell, selling, or importing a patented invention without consent of the patent owner. 35 U.S.C. § 271(a). Determining patent infringement is a two-step process. Once the claims have been construed, the second step is to compare the construed claims to the accused device. This comparison is a question of fact. *Advanced Cardiovascular Sys. v. SciMed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001). To prove direct infringement, a complainant must establish by a preponderance of the evidence that one or more claims of the patent read on the

accused device either literally or under the doctrine of equivalents. *See Certain Network Devices, Related Software & Components Thereof (II)*, Inv. No. 337-TA-945, Comm'n Op., 2018 WL 8648380, at *5 (Jul. 12, 2018) (citing *SciMed*, 261 F.3d at 1336); 19 C.F.R. § 210.37(a) ("The proponent of any factual proposition shall be required to sustain the burden of proof with respect thereto.").

C. Invalidity Under 35 U.S.C. § 103 (pre-AIA)[9]

While "[a] patent shall be presumed valid[,]" 35 U.S.C. § 282, this presumption of validity may be overcome by "clear and convincing evidence." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007).

A patent claim is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. To determine whether a claimed invention would have been obvious at the time of the invention, one must consider: "(1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations, including commercial success, long felt but unsolved needs, and failure of others." *Dystar*

[9] The law prior to the enactment of the Leahy-Smith America Invents Act ("AIA") applies here because the effective filing date of the '631 Patent is before March 16, 2013. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 n.4 (Fed. Cir. 2016).

Textilfarben GmbH v. C.H. Patrick Co., 464 F.3d 1356, 1361 (Fed. Cir. 2006) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

Multiple prior art references may be used in combination. *PharmaStem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). To avoid the temptation of reasoning in hindsight, a party asserting obviousness in light of a combination of references must "show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, . . . and would have had a reasonable expectation of success in doing so." *Id.*; *see KSR Int'l, Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1739-42 (2007) (rejecting earlier "teaching, suggestion, or motivation" test in favor of a more "expansive and flexible approach").

A motivation to combine does not need to be made explicit. "It is well settled that, even where references do not explicitly convey a motivation to combine, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *ABT Sys., LLC v. Emerson Elec. Co.*, 797 F.3d 1350, 1360 (Fed. Cir. 2015) (quoting from *KSR*). For example, "a court may find a motivation to combine prior art references in the nature of the problem to be solved." *Id.* Similarly, where one of skill can recognize that application of something in the prior art can improve the performance of a prior art device, that recognition may supply the apparent reason to combine the prior art or modify it. *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1003 (Fed. Cir. 2016) ("For the technique's use to be

obvious, the skilled artisan need only be able to recognize, based on her background knowledge, its potential to improve the device and be able to apply the technique.")

Evidence of secondary consideration of non-obviousness can overcome a case of obviousness and must be considered when present. *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017). The burden of showing the existence and applicability of secondary considerations is on the patentee and, as such, the patentee must establish a nexus between the evidence and the merits of the claimed invention. *Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1068 (Fed. Cir. 2016). However, a *prima facie* case is generally set forth "when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed. Cir. 2004) (*quoting Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988)); *Certain Crystalline Cefadroxil Monohydrate*, Inv. No. 337-TA-293, Comm'n Op. (March 15, 1990).

D. Written Description

35 U.S.C. § 112, ¶ 1 (pre-AIA) requires that "[t]he specification shall contain a written description of the invention." "That requirement is satisfied only if the inventor conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrates that by disclosure in the specification of the patent." *Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1376–77 (Fed. Cir.

2019) (internal citations and quotation marks omitted) ("*Nuvo Pharm.*"). "The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014); *Certain UV Curable Coatings for Optical Fibers, Coated Optical Fibers, and Products Containing Same*, Inv. No. 337-TA-1031, Comm'n Op., at 9 (Jun. 7, 2018) (public vers.) (the written description requirement "is part of the *quid pro quo* of the patent grant and ensures that the public receives a meaningful disclosure in exchange for being excluded from practicing an invention for a period of time") ("*UV Curable Coatings*").

E. Enablement

Separate and apart from the written description requirement, 35 U.S.C. § 112, ¶ 1 (pre-AIA) also requires that the specification describe "the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the [the invention]." The "enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *Automotive Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1282 (Fed. Cir. 2007) (internal quotation marks and citations omitted). This is not to say that the specification must expressly spell out every possible iteration of every claim,

because "the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art." *See Trustees of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018) (internal quotation and citation omitted).

Factors to be considered in determining whether the experimentation necessary to practice the claimed invention is "undue," include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).[10] "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Id.*

F. Inventorship

Under 35 U.S.C. § 102(f) (pre-AIA), a person is not entitled to a patent if "he did not himself invent the subject matter sought to be patented." Thus, a patent is invalid for improper inventorship "if more or less than the true inventors are named." *Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1301 (Fed. Cir. 2002).

[10] The case law sometimes refers to these as the "*Wands* factors." *See e.g. Storer v. Clark*, 860 F.3d 1340, 1345 (Fed. Cir. 2017) ("Storer does not dispute the Board's findings as to the third, fourth, fifth, sixth, and eighth *Wands* factors, but argues that these factors are not dispositive of enablement.")

To show that an allegedly omitted inventor was a joint inventor, it must be shown that the alleged joint inventor "(1) contribute[d] in some significant manner to the conception or reduction to practice of the invention, (2) ma[de] a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and (3) d[id] more than merely explain to the real inventors well-known concepts and/or the current state of the art." *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998). Moreover, "for the conception of a joint invention, each of the joint inventors need not 'make the same type or amount of contribution' to the invention. 35 U.S.C. § 116. "One need not alone conceive of the entire invention, for this would obviate the concept of joint inventorship. However, a joint inventor must contribute in some significant manner to the conception of the invention." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997); *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998) ("[E]ach [joint inventor] needs to perform only a part of the task which produces the invention"). And a person need only contribute to a single claim to be considered a joint inventor. *See* 35 U.S.C. § 116(a) ("Inventors may apply for a patent jointly even though … each did not make a contribution to the subject matter of every claim of the patent").

The Federal Circuit has explained that being a joint inventor requires contributing to the *conception* of the invention, not merely the reduction to practice:

> [O]ne does not qualify as a joint inventor by merely assisting the actual inventor after conception of the claimed invention. One who simply provides the inventor with well-known principles or explains the state of the art without ever having a firm and definite idea of the claimed combination as a whole does not qualify as a joint inventor. Moreover, depending on the scope of a patent's claims, one of ordinary skill in the art who simply reduced

> the inventor's idea to practice is not necessarily a joint inventor, even if the specification discloses that embodiment to satisfy the best mode requirement.

See Ethicon, 135 F.3d at 1460 (internal citations and quotation marks omitted).

G. Prior invention by another

Under 102(g)(2) (pre-AIA), a patent is invalid if prior to the date of invention, "the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it." *See* 35 U.S.C. § 102(g)(2) (pre-AIA); *Apotex USA, Inc. v. Merck & Co.*, 254 F.3d 1031, 1035 (Fed. Cir. 2001) (explaining that "§ 102(g) may be asserted as a basis for invalidating a patent in defense to an infringement suit").

The test for establishing a reduction to practice (*i.e.* whether the invention was "made") requires that the prior inventor must have (1) constructed an embodiment or performed a process that met all the claim limitations and (2) determined that the invention would work for its intended purpose. *See Fox Grp., Inc. v. Cree, Inc.*, 700 F.3d 1300, 1305 (Fed. Cir. 2012). But "an accidental, unappreciated reduction to practice should not constitute a 'true' reduction to practice for the purposes of … anticipation pursuant to section 102(g)." *See Mycogen Plant Sci. v. Monsanto Co.*, 243 F.3d 1316, 1336 (Fed. Cir. 2001). That being said, "[t]he reduction to practice test does not require *in haec verba* appreciation of each of the" claim limitations. *Id.* at 1336. Thus, it is sufficient to provide evidence that a product or process met all the limitations of the claims and that the resulting

product was "appreciated to work for its intended purpose." *Id.* at 1337 (explaining that prior inventors "actions were clearly performed deliberately, with no suggestion of accidental invention").

While the language of § 102(g)(2) does not contain an "explicit [public] disclosure requirement," the Federal Circuit has explained that "the spirit and policy of the patent laws encourage an inventor to take steps to ensure that the public has gained knowledge of the invention which will insure its preservation in the public domain or else run the risk of being dominated by the patent of another." *Apotex*, 254 F.3d at 1038 (internal quotation marks and citations omitted); *see also W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed.Cir.1983) ("Early public disclosure is a linchpin of the patent system. As between a prior inventor [who does not disclose] and a later inventor who promptly files a patent application ..., the law favors the latter."). Thus, "absent a satisfactory explanation for the delay or the presence of other mitigating facts, a prior invention will therefore be deemed suppressed or concealed within the meaning of § 102(g) if, within a reasonable time after completion, no steps are taken to make the invention publicly known." *Apotex*, 254 F.3d at 1038.

There is no particular length of delay in public disclosure that is per se unreasonable. *Checkpoint Sys., Inc. v. U.S. Int'l Trade Comm'n*, 54 F.3d 756, 761 (Fed. Cir. 1995) "Rather, a determination of abandonment, suppression, or concealment has consistently been based on equitable principles and public policy as applied to the facts of each case," and thus a "court must determine whether,

under the facts before it, any delay was reasonable or excused as a matter of law." *Id.* (internal quotation marks and citations omitted). Moreover, a prior inventor can abandon, suppress, or conceal the invention for a time after the reduction to practice as long as that inventor "resumed activity (*i.e.*, made the benefits of its invention known to the public)" before the later inventor's entry into the field. *Apotex*, 254 F.3d at 1039–40.

Public disclosure can be shown through, *e.g.*, filing a patent application, or commercializing a product. *Fox Grp.*, 700 F.3d at 1306. And "[i]n cases in which an invention is disclosed to the public by commercialization, courts have excused delay upon proof that the first inventor engaged in reasonable efforts to bring the invention to market." *Checkpoint*, 54 F.3d at 761–62.

H. Domestic Industry

Section 337 requires that an industry in the United States be established or be in the process of being established. *See* 19 U.S.C. § 1337(a)(2). For a patent-based claim, this domestic industry requirement consists of what are often called the "technical prong" and the "economic prong." *See*, *e.g.*, *Certain Computers and Computer Peripheral Devices, and Components Thereof, and Products Containing Same*, Inv. No. 337-TA-841, Comm'n Op., at 26 (Jan. 9, 2014).

The technical prong of the domestic industry requirement is satisfied when it is determined that the complainant practices at least one claim of each asserted patent. *Id.* The test for determining whether a complainant practices a claim of a patent at issue is essentially the same as that for infringement, *i.e.*, it requires that

a complainant's domestic product practice each limitation of a claim. *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1375 (Fed. Cir. 2003).

The "economic prong" is defined in Section 337(a)(3), and provides the following criteria for determining whether a domestic industry exists:

> [A]n industry in the United States shall be considered to exist if there is in the United States, with respect to the articles protected by the patent, copyright, trademark, or mask work concerned—
>
> (A) significant investment in plant and equipment;
>
> (B) significant employment of labor or capital; or
>
> (C) substantial investment in its exploitation, including engineering, research and development, or licensing.

19 U.S.C. § 1337(a)(3). To satisfy the economic prong of the domestic industry requirement, a complainant need only demonstrate that any one of the three criteria set forth under subsection (a)(3) is satisfied. *See Certain Variable Speed Wind Turbines & Components Thereof,* Inv. No. 337-TA-376, Commission Opinion at 21 (Sept. 23, 1996).

The Commission has emphasized that "there is no minimum monetary expenditure that a complainant must demonstrate to qualify as a domestic industry." *Certain Stringed Musical Instruments and Components Thereof,* Inv. No. 337-TA-586, Comm'n Op. at 25 (May 16, 2008). Further, "there is no need to define or quantify the industry itself in absolute mathematical terms." *Id.* at 26.

Determining whether an investment is "substantial" or "significant" under 19 U.S.C. § 1337(a)(3) is context-dependent. *Certain Printing and Imaging Devices and Components Thereof,* Inv. No. 337-TA-690, Comm'n Op. at 31 (Feb. 17, 2011)

("*Printing and Imaging Devices*"); *see also Lelo Inc. v. International Trade Comm'n*, 786 F.3d 879, 883-84 (Fed. Cir. 2015). Thus, "the magnitude of the investment cannot be assessed without consideration of the nature and importance of the complainant's activities to the patented products in the context of the marketplace or industry in question." *Printing and Imaging Devices*, at 31. Quantitative analysis of investments is required, but "qualitative evidence, while not sufficient on its own, supports a finding of significant" investments. *See Certain Collapsible Sockets for Mobile Electronic Devices and Components Thereof*, Inv. 337-TA-1056, Comm'n Op., at 20 (Jul. 9, 2018).

With all that said, it is important to bear in mind that "[t]he purpose of the domestic industry requirement is to prevent the ITC from becoming a forum for resolving disputes brought by foreign complainants whose only connection with the United States is ownership of a U.S. patent." *Battery-Powered Ride-On Toy Vehicles*, Inv. No. 337-TA-314, USITC Pub. 2420, Initial Det. at 18-21 (Aug. 1991). Genuine domestic industries with connections to the United States are to be protected. Accordingly, the Commission has adopted a "flexible, market oriented approach" to the question of whether a domestic industry exists, favoring a case-by-case determination "in light of the realities of the marketplace." *Certain Wireless Devices with 3G and/or 4G Capabilities & Components Thereof*, Inv. No. 337-TA-868, Initial Det., at 128 (Jun. 13, 2014) (citing *Certain Dynamic Random Access Memories*, Inv. No. 337-TA-242,USITC Pub. 2034, Comm'n Op. at 62 (Nov. 1987)), *unreviewed in relevant part*.

IV. U.S. PATENT NO. 9,220,631

A. Claim Construction

1. Level of skill of a Person of Ordinary Skill in the Art

Novartis's and Regeneron's different definitions of a person of ordinary skill in the art ("POSITA") in the art are set out in their respective briefs. (CPreBr. at 23-25; RPreBr. at 58-59.) Both private parties appear to agree that a slightly different definition is appropriate for the dependent method claims 24-25, in that a POSITA would be an ophthalmologist with experience with intravitreal injections. (*Id.*)

In the Staff's view, there is no material difference between the two definitions (including the alternative criteria for claims 24-25) and either definition appears appropriate. On balance, the Staff believes the evidence may slightly favor Regeneron's definition in that it does not contain the requirement in Novartis's definition that a POSITA have been a member of a product development team. The Staff's view is that such a requirement is too narrow in that it may exclude persons with primarily academic, as opposed to industry, experience, as academics are not necessarily engaged in developing products. The Staff does not necessarily disagree with Novartis's contention that either academics or those in industry may work in teams. For example, and as explained below, the evidence will show that the '631 patent was developed by a large team of engineers at Vetter and Novartis. (*See* Section IV.D.2.)

The Staff would also add to both definitions that relevant additional education could make up for a lack of work experience, and relevant additional work experience can make up for a lack of education.

Ultimately, the Staff agrees with Regeneron and Novartis that no issue in the investigation turns on which definition the ALJ chooses. (CPreBr. at 25; RPreBr. at 59.)

2. Terms with agreed constructions

In the Staff's view, there are no claim construction disputes for the ALJ to resolve. *See Eon Corp. IP Holdings v. Silver Spring Networks*, 815 F.3d 1314, 1319 (Fed. Cir. 2016) ("[A] district court's duty at the claim construction stage is, simply, the one that we described in *O2 Micro* and many times before: to resolve a dispute about claim scope that has been raised by the parties."); *see also O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1360 (Fed. Cir. 2008) ("When the parties raise an actual dispute regarding the proper scope of [the] claims, the court, not the jury, must resolve that dispute.") The parties did not dispute the definitions of any constructions during the *Markman* proceedings in this case; rather, Regeneron contended that several claim terms were indefinite. (EDIS Doc. ID 721764, Joint Disclosure of Proposed Claim Constructions.)

The parties also jointly proposed the following constructions (all of which appear in claims still at issue):

Claim Term for Construction	Agreed-to Construction
Claim 1: "VEGF-antagonist"	"A substance capable of blocking or inhibiting the biological action of vascular endothelial growth factor."
Claim 4: "the silicone oil is DC365 emulsion"	"The silicone oil is applied as a component of DC365 emulsion."
Claim 11: "non-antibody VEGF antagonist"	"A VEGF-antagonist that is not an antibody."

Beyond the jointly proposed constructions, the Staff believes the remaining claim terms can be given their plain and ordinary meaning.

a. "VEGF-antagonist" (claim 1)

The parties agree that "VEGF-antagonist" should be construed as "a substance capable of blocking or inhibiting the biological action of vascular endothelial growth factor." (JCC, at p. 3.) The specification does not define "VEGF-antagonist," but the parties' definition is consistent with how the term is used by prior art references included in the file history of the '631 Patent. *See Kumar v. Ovonic Battery Co.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003) ("Our cases also establish that prior art cited in a patent or cited in the prosecution history of the patent constitutes intrinsic evidence"). For example, "Ranibizumab," Scientific Discussion, EMEA, 2007, pp. 1-54, at 1 (CX-0128.0001, "Scientific Discussion"), states that the VEGF-antagonist Lucentis "binds with high affinity to VEGF-A isoforms" and thereby "prevents the interaction of VEGF-A with its receptors VEGFR-1 and

VEGFR-2 on the surface of endothelial cells."[11] Thus, a "VEGF-antagonist" is "a substance capable of blocking or inhibiting the biological action of vascular endothelial growth factor."

b. "the silicone oil is DC365 emulsion" (claims 1, 23)

The parties agree that "the silicone oil is DC365 emulsion" should be construed as "the silicone oil is applied as a component of DC365 emulsion." (JCC at p. 3.) The specification explains that DC365 is a Dow Corning silicone oil emulsion. ('631 patent, 5:9-12.) A Dow Corning FAQ from 2002, describes the emulsion as "composed of 35% *Dow Corning*® 360 Medical Fluid, 350 cSt in water…"[12] (RX-0430.0002.) Thus, the parties' proposed definition accurately captures that the claimed "silicone oil" is applied as one component of an emulsion of DC365.

c. "non-antibody VEGF antagonist" (claim 11)

The parties agree that "non-antibody VEGF antagonist" should be construed as "[a] VEGF-antagonist that is not an antibody." For example, Lucentis is an antibody VEGF-antagonist ('631 patent, 6:33-36), and specifically, "a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by standard recombinant DNA technology." (CX-0128.0001.) Conversely, the patent

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[11] The '631 patent identifies Lucentis as an example of a VEGF-antagonist. ('631 patent, 4:19-27.)

[12] The centistoke (cSt) is a measurement of fluid viscosity. (RX-510.0013 ("Centistokes [:] A unit of kinematic viscosity abbreviated cst or cs. It is defined as the viscosity in centipoise (gm/cm – sec/100) divided by the density in gm/cc, when both are measured at the same temperature (30)").)

specification discloses a non-exhaustive list of non-antibody VEGF antagonists that share the property of not being antibodies. ('631 patent, 6:37 – 7:57.)

Although the Staff originally proposed to construe this term, and the parties have jointly agreed on a definition, on further review the Staff does not believe the term needs to be construed.

B. Infringement

Regeneron does not oppose a finding that the EYLEA PFS infringes claims 1, 3-6, 11-13, 16, 17, and 21-23, and that claims 24-25 are infringed by physicians who administer EYLEA PFS. (RPreBr. at 59; EDIS Doc. ID 735497, Regeneron Response to Novartis MSD, at p. 18.) Regeneron also does not oppose a finding that it indirectly infringes the '631 patent. (RPreBr. at 59.)

To the extent the ALJ does not grant Novartis's MSD that the asserted claims are infringed,[13] the Staff agrees with Novartis that the evidence will show that the EYLEA PFS infringes claims 1, 3-6, 11-13, 16, 17, and 21-23 of the '631 patent and that the administration of EYLEA PFS to a patient by a physician directly infringes claims 24-25 of the '631 patent.

The Staff has reviewed the evidence relied on by Novartis in its Pre-Hearing Brief. (CPreBr. at 32-35.) The Staff agrees that such evidence will show that the EYLEA PFS practices the asserted claims. For example, Novartis relies on various parts of the EYLEA PFS sBLA (*see e.g.* CX-0508C.0004, CX-0432C.0004; CX-

[13] EDIS Doc. ID 734529.

0492C.0033; CX-0519C.0007), the label for EYLEA PFS (CX-0402C.0001, 30), and the testimony of Regeneron's witnesses (JX-0403, Lamb Tr.; JX-0408C, Graham Tr.). The Staff generally agrees that the evidence cited in Novartis's Pre-Hearing Brief at pages 32-35 (*i.e.* footnotes 5-26) supports a finding of infringement for the asserted claims. The Staff also expects that Novartis's expert Mr. Leinsing will provide expert testimony as to why such evidence shows infringement of all the asserted claims other than 24 and 25 (the method of administration claims); Dr. Calman is expected to provide expert testimony explaining how physicians administering EYLEA PFS infringe claims 24 and 25. Thus, to the extent the ALJ does not grant Novartis's MSD, the Staff will rely on that evidence and expert testimony to show at the hearing that the asserted claims are infringed.

For claims 11 and 12, which require respectively "the VEGF antagonist is a non-antibody VEGF antagonist" and "the non-antibody VEGF antagonist is aflibercept or conbercept," Novartis's Pre-Hearing Brief cites only the '631 patent as evidence. (CPreBr. at 34, n. 17 & 18.) In the Staff's view, statements made by the patentee in the specification about the accused product are not sufficient evidence to support a finding of infringement. But it does not appear to be contested that the drug substance in EYLEA PFS is a non-antibody VEGF-antagonist, and expert testimony from Mr. Leinsing and evidence in record will show the same. (RX-0577.0001-2 (comparing the "antibody fragment" ranibizumab (*i.e.* Lucentis) to aflibercept, a "recombinant fusion protein").) Moreover, the evidence will show that

EYLEA is the brand name for the drug aflibercept, and therefore EYLEA PFS meets claim 12. (CX-0508C.0003.)

C. Domestic Industry - Technical Prong

1. Claims 1, 3-7, 16-17, 22, and 23 of the '631 patent

Regeneron does not oppose a finding that the BEOVU PFS practices claims 1, 3-7, 16-17, 22, and 23 of the '631 patent. (RPreBr. at 59; EDIS Doc. ID 735497, Regeneron Response to Novartis MSD, Response to Chart of Material Facts at Nos. 68-87.)

To the extent the ALJ does not grant Novartis's MSD that BEOVU practices claims 1, 3-7, 16-17, 22, and 23 of the '631 patent,[14] the Staff agrees with Novartis that the evidence will show that BEOVU PFS practices each of those claims.

The Staff has reviewed the evidence relied on by Novartis in its Pre-Hearing Brief. (CPreBr. at 42-45.) The Staff agrees that such evidence will show that the BEOVU PFS practices claims 1, 3-7, 16-17, 22, and 23 of the '631 patent. For example, Novartis relies on internal product specifications (*see e.g.* CX-0069; CX-0071C; CX-0073C; CX-0162C; CX-0133C), BEOVU testing certifications (CX-0125C), third party documents regarding the silicone oil emulsion in the BEOVU PFS (CX-0257; CX-0258; CX-0259), and the BEOVU PFS label (CX-0117C). The Staff generally agrees that the evidence cited in Novartis's Pre-Hearing Brief at pages 43-45 (*i.e.* footnotes 27-43) supports a finding that BEOVU PFS practices

[14] EDIS Doc. ID 734529.

claims 1, 3-7, 16-17, 22, and 23 of the '631 patent. The Staff also expects that Novartis's expert Mr. Leinsing will provide expert testimony as to why such evidence shows that BEOVU PFS practices those claims. Thus, to the extent the ALJ does not grant Novartis's MSD, the Staff will rely on that evidence and expert testimony to show at the hearing that BEOVU PFS practices claims 1, 3-7, 16-17, 22, and 23.

2. Claims 21, 24, and 25

Although claims 21, 24, and 25 are addressed in Novartis's Pre-Hearing Brief (CPreBr. at 45-48), Novartis notified the parties and the ALJ via email on March 16, 2021 that Novartis "will no longer be relying on claims 21, 24, and 25 of the '631 patent for the purposes of the technical prong." Thus, Novartis has affirmatively waived those arguments, and the Staff does not expect to address claims 21, 24, and 25 of the '631 patent for the purposes of the technical prong at the hearing.

D. Invalidity

1. Obviousness Under 35 U.S.C. § 103

Regeneron asserts four obviousness combinations:

- International Pat. Appl. Pub. No. WO 2011/006877 ("Sigg") (JX-0301) in view of International Pat. Appl. Pub. No. WO 2009/030976 ("Boulange") (JX-0302);
- Sigg in view of the [redacted] 1 mL [redacted] Syringe [redacted]

- International Pat. Appl. Pub. No. WO 2008/077155 ("Lam") (JX-0313) in view of Boulange or [redacted]; and
- Macugen PFS in view of Boulange or [redacted].

Novartis generally does not appear to contest that the prior art raised by Regeneron discloses each of the dependent claim limitations. Rather, Novartis argues (1) that a POSITA would not combine the references and/or would not be successful in doing so; (2) that [redacted] and Macugen PFS are not prior art; and (3) that secondary considerations require a finding of non-obviousness.[15]

As explained in more detail below, the Staff agrees with Regeneron that the claimed invention of the '631 patent would have been obvious over the asserted combinations.

a. The asserted prior art

(1) Sigg

Sigg is an International Patent Application Publication, WO 2011/006877, which was published on January 20, 2011. (JX-0301.0001.) Because that is more than one year before the '631 patent's October 2012 priority date, Sigg is prior art to the '631 patent. Sigg identifies the applicant as Novartis, and the single inventor as Jurgen Sigg, *i.e.* the same Dr. Sigg named as an inventor of the '631 patent. (JX-0301.0001.) Sigg discloses a method for terminally sterilizing "prefilled containers" and specifically, "prefilled containers containing sensitive solutions such as a drug

[15] As explained below, Novartis also raises a small number of discrete issues over allegedly missing elements from certain pieces of prior art.

product or biological therapeutic." (*Id.* 3:8-10.) Example 1 in Sigg discloses terminally sterilizing a PFS containing "[a] formulation as described in U.S. Patent No. 7,060,269." (*Id.* at 0021.) U.S. Patent No. 7,060,269 discloses ranibizumab, *i.e.* Lucentis. (JX-0517; JX-0301, 9:11-14; CPreBr. at 16.)

(2) Boulange

Boulange is an International Patent Application Publication, WO 2009/030976, which was published in 2009. (JX-0302.) Because that is more than one year before the '631 patent's October 2012 priority date, Boulange is prior art to the '631 patent. Boulange is a Becton Dickinson patent that discloses several syringes, including pre-filled syringes.[16] (*Id.* at 0001, 14:19-21.) Boulange also discloses a series of examples in which the break loose and glide forces of syringes internally coated with silicone oil or "Parylene C" are compared to un-siliconized syringes. (*Id.* at 18:15-19:10.) Parylene C is "polymer material" described in Boulange. (*Id.* at 2:7-20.)

(3) [redacted]

The [redacted] was a siliconized syringe offered for sale by [redacted] in the U.S. in 2011. (JX-0039C, Declaration of [redacted].").) Mr. [redacted], submitted a declaration during fact discovery

[16] Becton Dickinson, or "BD", is one the world's largest manufacturers of, among other things, syringes. (*See e.g.* JX-0272C,0001-9.); RX-0778.0001 (2020 article referring to BD as "the world's largest manufacturer of syringes").)

identifying certain documents about the [redacted] and identifying the relevant on-sale date for [redacted]. ([redacted] Decl., ¶ 1.) Specifically, Mr. [redacted] explains that "[redacted]" (JX-0007C) is a presentation entitled "[redacted]" which "reflected [redacted] technology and products available to customers at the time." (*Id.* at ¶ 3.) Mr. [redacted] explains that he sent a copy of JX-0007C to [redacted] customer [redacted] in 2011, as an attachment to a memorandum marked as "[redacted]" (JX-0010C), in order to explain the properties of the 1 ml and 1.5 ml [redacted] (*Id.* at ¶4.) Mr. [redacted] asserts that "pages marked [redacted] [JX-0007C.0002-0006] depict certain characteristics of the 1ml [redacted] including the amount of silicone oil that is baked onto the syringe and the resulting activation and gliding forces." (*Id.*) Mr. [redacted] also identified JX-0008C, a 2011 price quote to [redacted] for the "[redacted]," and JX-0009C, a 2009 [redacted] purchase order. (*Id.* at ¶ 5.) Mr. [redacted] explains that [redacted] ultimately purchased the 1.5 ml syringe, but that the same baked-on siliconization technology was "characterized in a 1 mL syringe which was also available at least as of May 20, 2011." (*Id.*)

Novartis asserts that despite this evidence, the [redacted] is not prior art because it was not on sale in the U.S. and any syringe that may have been on sale did not have between 1 and 100 μg of silicone oil as required by the claims. (CPreBr. at 128-137.) The Staff disagrees.

Novartis argues that neither the memorandum (JX-0010C, which Novartis refers to as the '[redacted] nor the slide deck (JX-0007C) show that the [redacted] was on sale in the U.S. (CPreBr. at 128-133.) With respect to the slide deck, the Staff notes that the [redacted] price quote (JX-0008C) and purchase order (JX-0009C) both refer to [redacted]

JX-0008C.0001 (annotated)

JX-0009C.0001 (annotated)

And the slide deck appears to show test results for that product indicating glide forces of less than 10N:

JX-0007C.0014.

Thus, based on this connection between the slide deck and the purchase order in 2009 and the price quote in 2011, the Staff believes the slide deck does provide some circumstantial evidence of a baked-on silicone syringe for sale in the U.S. (if not direct evidence of the sale of the alleged prior art 1.0 ml).

Moreover, the also provides circumstantial evidence of an offer for sale. It is clear from the price quote (JX-0008C) and the purchase order (JX-0009C) that in 2009-2011 was a and was being offered, or actually buying, ' " syringes.[17] Although both are international companies, the price quote, purchase order, and letter all appear to involve the U.S. based sections of the companies, *i.e.*

[17]

[redacted]. (JX-0008.0001, 0003; JX-0009.0001; JX-0010.0001.) Thus the 2011 [redacted], which concerns "[redacted]" (JX-0010C.0001 (emphasis added)), is a letter from a supplier [redacted] to a U.S. customer ([redacted] concerning a [redacted] syringe that used baked silicone. In the Staff's view, that is additional circumstantial evidence that certain [redacted] syringes were on sale in the U.S. in 2011.

While alone the slide deck and letter might not directly establish the sale of the [redacted], both pieces of evidence (along with the purchase order and price quote) corroborate the more relevant direct evidence: the declaration of Mr. [redacted] Mr. [redacted] declared, under penalty of perjury,[18] that a [redacted] was on sale in the U.S. in 2011, and that the pages at JX-0007C.0002-0006 identify the "amount of silicone oil that is baked onto the syringe and the resulting activation and gliding forces." ([redacted] Decl. at ¶ 4.) Mr. [redacted] also explained that the price quote (JX-0008C) and the purchase order (JX-0009C) were directed to the 1.5 ml version of the product, but that "the same baked on silicone oil technology had been developed and characterized in a 1 mL syringe which was also available at least as of May 20, 2011 as described in" JX-0007C-0002-0006. ([redacted] Decl. at ¶ 5.)

[18] [redacted] Decl. at JX-0039C.0002 ("I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge").

Novartis attempts to contradict this evidence with a somewhat complex argument involving the letter and the slide deck, and whether the syringes being offered to [redacted] were made in [redacted]. (CPreBr. at 129-132, 137-138.) The argument appears to be that it is not clear from the letter or slide deck whether any syringes being offered to [redacted] in the U.S. were made in [redacted], and syringes made in the two different locations had different amounts of silicone oil (and may have been only development projects in either location, as opposed to commercially available syringes). But while the letter and slide deck may not clarify which syringes were on sale in the U.S., the Staff is not aware of any evidence within the letter or slides that *contradicts* Mr. [redacted] simple testimony that syringes with the properties identified at JX-0007C.0002-0006 were available for sale in the U.S. in 2011, nor does Novartis identify any such evidence. As Mr. [redacted] explained, the slides and letter were intended to explain to [redacted] the technology of certain [redacted] that were on sale in the U.S. in 2011. ([redacted] Decl. at ¶ 4.)

Moreover, the Staff is not aware of any reason to doubt Mr. [redacted] credibility.[19] Mr. [redacted] is a [redacted]" and does not appear to have any personal stake in the outcome of this case. (Moyer Decl. at ¶ 1.) Similarly, [redacted]

[19] The Staff notes that Novartis had the opportunity to pursue a deposition of Mr. [redacted] during fact discovery but did not do so. If Novartis had concerns about Mr. [redacted] credibility, it effectively waived the right to raise those concerns by deciding not to depose him.

and the Staff is not aware of [redacted] having any interest in the outcome of the investigation. Novartis presents no evidence to show that Novartis's or Dr. Hanes's interpretation of the letter and slides that Mr. [redacted] sent are likely to be more accurate than Mr. [redacted] own explanation about the same. Mr. [redacted] after all, was a percipient witness to the events. Novartis and Dr. Hanes were not. Therefore, the Staff does not believe the evidence will show any reason to doubt the credibility or accuracy of Mr. [redacted] declaration.

Finally, Novartis also incorrectly asserts that Mr. [redacted] "does not explain which syringes supposedly were offered for sale in the United States in 2011." (CPreBr. at 134.) His declaration explains that syringes having the properties at JX-0007C.0002-0006 were available for sale in the U.S. in 2011. ([redacted] Decl. at ¶ 4.) Moreover, the cited slides all refer to the same [redacted] To the extent the slides refer to individual syringes with different amounts of silicone, every syringe had silicone oil within the ranges claimed by the '631 patent, and break loose forces less than 11N. (JX-0007C.0002-0006.) Moreover, the Staff notes that Novartis's expert Mr. Leinsing testified at the *Markman* hearing in this matter that there would always be variation in the amount of silicone oil on syringes in the same batch, even if all the syringes were targeting the same specified amount:

> **Q:** So am I correct that, for any given syringe in a production batch of syringes, it would specify to have that amount of silicone, you are going to have some variation of the amount of silicone in each individual syringe, even though they might have a single average or a single specified number; is that correct?

> **Mr. Leinsing:** Yes. So you can even specify a range for the silicone for applying to the syringes, but then even within a given syringe, you're going to have variability within that syringe. So then we talk about an average, and then the variability within that particular syringe. That's where that plus or minus 10 percent would come into play.
>
> **Q:** So is it fair to say that a person of skill in the art in this field would recognize that it's simply not possible, at least on the level of an individual syringe, to achieve the exact amount of silicone, one exact amount for every syringe that you make?
>
> **Mr. Leinsing:** Yeah. It would not be possible to have an exact amount on one syringe, or even from syringe to syringe. You would not be able to achieve that. It wouldn't be realistic or reasonable to expect that.

(EDIS Doc. ID 727758, *Markman* Hearing Tr., at 152:14-153:10.)

Thus, the Staff believes that Mr. [redacted] declaration, corroborated by the [redacted], the slide deck, the price quote, and the purchase order, will show that the [redacted] with the properties shown at JX-0007C.0002-0006 was being offered for sale in the U.S. by [redacted] as of May 2011, and is therefore prior art to the '631 patent.

(4) Macugen PFS

"Macugen" is the trade name for a pre-filled syringe containing a pegaptanib sodium injection, a VEGF-antagonist first approved for sale by the FDA in 2004 to treat wAMD via intravitreal injection ("Macugen PFS"). (JX-0005C.0001.) Expert testimony from Dr. Kiss is expected to show that ophthalmologists were using Macugen PFS to treat patients with wAMD at least as early as 2007-2009. (JX-0450.0002; JX-0372.0001.) Thus, because Macugen PFS was on sale more than one year before October 2012, it is prior art to the '631 patent.

Although Novartis does not dispute that Macugen PFS was on sale before the priority date, Novartis contends that a terminally sterilized Macugen PFS is not prior art. (CPreBr. at 151.) As explained in more detail below, the Staff believes as a factual matter that the evidence will show that Macugen PFS was terminally sterilized as of 2008. But the Staff responds here to Novartis's legal argument that Macugen PFS is not prior art available for a § 103 obviousness combination because it was not publicly known that Macugen PFS was terminally sterilized. (CPreBr. at 151.) In the Staff's view, that position is inconsistent with Federal Circuit case law regarding the use of "on sale" prior art under § 102(b) (pre-AIA) in an obviousness combination.

The Federal Circuit has frequently explained that "[p]rior art under the § 102(b) on-sale bar is also prior art for the purposes of obviousness under § 103." *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1344 (Fed. Cir. 2007); *see also TorPharm, Inc. v. Ranbaxy Pharm., Inc.*, 336 F.3d 1322, 1327 (Fed. Cir. 2003) (explaining that on-sale prior art used in an obviousness combination has "been termed the '§§ 102(b)/103' bar to patentability"); *LaBounty Mfg. v. Int'l Trade Comm'n*, 958 F.2d 1066, 1071 (Fed.Cir.1992) ("Section 102(b) may create a bar to patentability ... in conjunction with [§ 103], if the claimed invention would have been obvious from the on-sale device in conjunction with the prior art."); *Baker Oil Tools, Inc. v. Geo Vann, Inc.*, 828 F.2d 1558, 1563 (Fed. Cir. 1987) ("If a device was in public use or on sale before the critical date, then that device becomes a reference under section 103 against the claimed invention"). And under the § 102(b) on-sale

bar, it does not matter whether the properties of the prior art device were known to the parties involved in the sale. As the Federal Circuit has explained, "[i]f a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics. *Abbott Lab'ys v. Geneva Pharm., Inc.*, 182 F.3d 1315, 1319 (Fed. Cir. 1999); *accord Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc.*, 139 S. Ct. 628, 633 (2019) (characterizing Federal Circuit rule "that 'secret sales' can invalidate a patent" as "settled pre-AIA precedent on the meaning of 'on sale'"); *accord City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 136 (1877) ("It is not a public knowledge of his invention that precludes the inventor from obtaining a patent for it, but a public use or sale of it.")

Here, Regeneron and the Staff contend that Macugen PFS was on sale more than one year prior to October 2012, and that the Macugen PFS that was on sale was terminally sterilized. The case law cited above shows that whether a POSITA (or anyone else) purchasing Macugen PFS at the time *recognized* that it was terminally sterilized is irrelevant for the purposes of whether Macugen PFS is § 102 (b) (pre-AIA) "on sale" prior art available for use in an obviousness combination.

In support of its argument to the contrary, Novartis cites to *Quantachrome Corp. v. Micromeritics Instrument Corp.*, 15 F. App'x 848, 849 (Fed. Cir. 2001). (CPreBr. at 151.) But the devices at issue there "the Gulf Oil and Quantachrome pycnometers" (*Quantachrome* at 15 F. App'x at 850) were not on sale. Rather, the

district court found that "the Gulf Oil pycnometer project amounted to no more than private experimentation" and was never on sale, and the "Ultrapycnometer [*i.e.* the Quantachrome pycnometer] drawings do not qualify as relevant prior art" because "[a]ll of these drawings were kept in the private files of Quantachrome and were never disclosed to the public." *See Quantachrome Corp. v. Micromeritics Instrument Corp.*, 97 F. Supp. 2d 1181, 1187 (S.D. Fla. 2000). The Federal Circuit affirmed that part of the lower court's decision, holding that "substantial evidence supports the trial court's conclusion that these devices were kept confidential, and thus were not prior art." *Quantachrome* at 15 F. App'x at 850. Here of course, the Macugen PFS was not a "private experiment" and was not kept confidential but was on sale to the public before the priority date of the '631 patent. *Quantachrome* is thus inapposite.

Novartis also cites *BASF Corp. v. SNF Holding Co.*, 955 F.3d 958, 967 (Fed. Cir. 2020) as holding that "public sale or use of product does not render undisclosed features (e.g., the process of manufacture) prior art for obviousness." But that is not an accurate summary of the holding of *BASF Corp.* In *BASF Corp.* the Federal Circuit held that with respect to an alleged prior "public use" of the patented method "a third party's sale of products made by a secret process, more than one year before the critical date, does not create a bar to another inventor patenting the process." *BASF Corp.*, 955 F.3d at 967. In other words, this issue was an alleged "public use" under § 102(b), not the "on-sale" bar; the law is different for those different parts of the statute. This difference is illustrated by *BASF Corp.*, as the court separately held that a license to use the prior art process did not trigger the

on-sale bar because "the essential features of the claimed process here were not embodied in a product sold or offered for sale before the critical date." *Id.* at 970. *BASF* is thus inapposite because Macugen PFS is being asserted as a prior art device that was on sale more than a year before the priority date of the '631 patent; neither the claims nor the prior art involve a process and the various legal issues regarding a "public use" are not at issue.[20]

While the Staff disagrees with Novartis's legal argument, the Staff also notes that factually the evidence will show that while a POSITA may not have been able to determine the precise means by which Macugen PFS was terminally sterilized, that does not necessarily mean a POSITA would not have known that Macugen PFS was terminally sterilized. For example, the Macugen PFS label indicated it was provided in a "sterile foil pouch." (JX-0303.0008.) And the Macugen PFS was fitted with a [redacted] that was [redacted] (JX-0004C.0058.) While a POSITA would not have access to that description in the supplemental NDA, a POSITA would have seen the plastic clip in the product that was on sale. (JX-0303.007 (first step of administration is to "Remove the syringe from the plastic clip").) Between the "sterile foil pouch" language, the plastic clip, and the [redacted] (*i.e.* similar to the disclosed but

[20] The Staff notes that the evidence will show that Macugen PFS, was, in fact, in public use because physicians were using Macugen PFS to treat wAMD before the '631 patent's priority date. (JX-0372.0001.)

unclaimed design in the '631 patent), a POSITA could reasonably have deduced that the Macugen PFS was terminally sterilized. (Sigg Tr., at 140:4-7, 14-20.) Thus, while the Staff does not believe it relevant whether it was publicly known that Macugen PFS was terminally sterilized, the Staff believes the evidence will show that a POSITA could reasonably have determined based on examining the product and its label that Macugen PFS was in fact terminally sterilized.

Thus, the Staff's view is that the evidence will show that Macugen PFS was on sale more than one year before October 2012 and is therefore prior art to the '631 patent.

b. Sigg in view of Boulange

(1) Claim 1

1[preamble] A pre-filled, terminally sterilized syringe for intravitreal injection, the syringe comprising a glass body forming a barrel, a stopper and a plunger and containing an ophthalmic solution which comprises a VEGF-antagonist, wherein:

The Staff expects that the evidence will show that Sigg and Boulange disclosed pre-filled syringes. (Sigg at 1:5-8, 7:26-28, 9:1-3, 20:11-16; Boulange at 14:19-20.)

Sigg and Boulange both disclose that pre-filled syringes may be made of glass. (Sigg at 22:8-10; Boulange at 9:21-35, 13:9-12, 16:7-9, 22:4-5.) It was known in the art that glass was the preferred material for prefilled syringes. (JX-0298.002, Shah 2009 ("Prefilled syringes have traditionally been made of a glass body formed from USP type 1 borosilicate glass"); JX-0491.0003 ("Prefilled syringes, like vial dosage forms, are comprised of glass and elastomeric components");RX-0601.0002.)

Additionally, the Staff expects expert testimony to show that syringes were generally made of either glass or plastic, and it would have be an obvious design choice to pick one or the other.[21] *See KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.")

The PFS disclosed in Sigg comprises a barrel (102), a stopper, and a plunger. (Sigg at Fig. 1.) Sigg discloses that Example 1 involved a pre-filled syringe containing the VEGF-antagonist Lucentis for intravitreal injection, wherein the syringe was terminally sterilized using vaporized hydrogen peroxide ("VHP"), *i.e.* H_2O_2. (Sigg at 9:9-14, 20:9-18, claim 3 ("The method of claim 1 or claim 2 wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab"); JX-0517.)

[21] RX-0601.0002, Eakins 2007 ("The choice between glass and plastic – my view is that both have advantages and disadvantages and pharmaceutical companies should conduct their initial revue [sic] of both glass and plastic pre-fillable syringe options taking into account not only material compatibility with their drug but other factors such as availability and lead time for the delivery of samples")."); CX-0066 (ISO 11040-4 standard for Prefilled syringes – Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling); RX-0475 ("Although plastic prefilled syringes are gaining in popularity in Europe, glass barrels are still preferred in the United States: 99% of the prefillable syringes sold in the US by BD are its Hypak prefillable glass syringe. Glass is heavily favored primarily because it has been part of the industry for a long period of time").

1(a) the syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml,

Sigg discloses a PFS with a 0.5 and 1.0 ml nominal fill volume. (Sigg at 20:20-21; 22:8-10.) Boulange also discloses a 1.0 ml syringe. (Boulange at 14:19-21.)

1(b) the syringe barrel comprises from about 1 µg to 100 µg silicone oil,

Sigg does not disclose whether or what amount of silicone oil was deposited on the interior of the syringe barrel, although the '631 patent admits that it was known that syringes for intravitreal injection (such as those in Sigg) were known to "typically" require siliconization for "ease of use." ('631 patent at 4:48-60.) Thus, a POSITA would have understood that the syringe for intravitreal injection disclosed in Sigg would be siliconized.

Boulange discloses in Example 5 that 1 mL syringes were siliconized at a "rate of 40 µg for a surface area of 10 cm^2" or 4 µg per 1 cm^2, and that the silicone oil was baked onto the internal surface body of the syringe (*i.e.* an emulsion was applied). (Boulange at 20:15-17, Table 7.) The Staff expects that expert testimony from Mr. Koller will show that a 1 ml syringe (such as that disclosed in Boulange) has an internal surface area of approximately 10 cm^2. Thus, Boulange discloses syringes with an internal coating of silicone oil of approximately 40 µg, which is between the claimed 1-100 µg.

Novartis argues that Boulange does not disclose this limitation because the amount of silicone oil was "most likely done using a solvent extraction method," *i.e.* by measuring the amount of free silicone oil dissolved in a solvent following rinsing

the syringe with the solvent to extract the silicone. (CPreBr. at 126.) The Staff disagrees with this argument for at last two reasons.

First, the argument is contrary to the disclosure of Boulange. Boulange states that the syringes in Example 5 were siliconized at a "*rate* of 40 µg for a surface area of 10 cm^2". (Boulange at 20:15-17 (emphasis added); *see also id.* at Table 7 (showing results for syringes with 4 µg of silicone oil per cm^2).) The Staff expects that expert testimony will show that measuring the amount of silicone in a syringe may be done by measuring the amount applied, *i.e.* a rate expressed as an amount over a given surface area multiplied by total surface area or an amount over time multiplied by the total time. Conversely there is no disclosure in Boulange that the silicone was measured via a solvent extraction technique.

Additionally, Boulange's statement that "[t]he silicone amount was measured prior to any AGF test" (*i.e.* silicone was measure before the force tests) does not mean that a solvent extraction test was used. Expert testimony is expected to show that because solvent extraction removes silicone oil, it would make it impossible to run the break loose force tests on syringes where the silicone amount was measured with solvent extraction.[22] (CX-1184C, Koller Tr., at 250:13-251:8.) Thus, the Staff believes it more likely that Boulange measured the amount of silicone based on the rate of application, which is what is facially disclosed by Boulange's use of the word

[22] Mr. Koller is also expected to testify that the recovery rates for the solvent extraction methods known at the time would have been up 95%, *i.e.* even for a baked-on coating solvent extraction could remove 95% of the silicone. (CX-1184C, Koller Tr., 254:17-255:8; JX-0010C.0002).

"rate," and which the evidence will show was a known non-destructive method of measuring the amount of silicone oil on a syringe. Alternatively, another non-destructive testing method would be differential weighing, which a POSITA would also understand as being in accord with Boulange's disclosure of performing a non-destructive silicone characterization method prior to break loose force testing. ('631 patent, 5:5-9; RX-0430.000 ("Comparative testing of siliconized versus non-siliconized items is of course an obvious method of qualitative and quantitative assessment").)

Second, assuming for the sake of argument that Novartis is correct that the silicone oil in Boulange was measured with a solvent extraction test, it would be of no legal consequence because the claims of the '631 patent do not require any specific test to measure the silicone oil in the syringe and thus the specific test used cannot differentiate the claims from the prior art. *See Mettler-Toledo, Inc. v. B-Tek Scales, LLC,* 671 F.3d 1291, 1298 (Fed. Cir. 2012) ("Mettler also argues that Avery fails to teach moving a weight around the scale to calibrate the system. Because the claims do not require moving a weight around the scale, Avery need not expressly teach this particular calibration technique"); *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1308–09 (Fed. Cir. 2006) (absence in prior art public use of an unclaimed feature of the claimed invention did not avoid a finding of obviousness). The specification discloses that "[m]ethods for measuring the amount of silicone oil in such a syringe barrel are known in the art." ('631 patent, 5:5-7.) And among the two prior art methods that the '631 patent specifically identifies is "quantitation by

infrared-spectroscopy of the oil diluted in a suitable solvent," *i.e.* measuring by solvent extraction.[23] (*Id.*, at 5:7-9.) If Boulange discloses a prefilled syringe with 40 µg of silicone oil measured by the solvent extraction method, that is within the scope of what is claimed by the '631 patent, and thus anticipates that particular limitation.[24]

1(c) the VEGF antagonist solution comprises no more than 2 particles >50 µm in diameter per ml and …

The Staff expects the evidence will show that the limitation "2 particles >50 µm" comes from the USP-789 standard. ('631 patent, 6:27-28 ("USP789 (United States Pharmacopoeia: Particulate Matter in Ophthalmic Solutions)"); CX-0065.0007 at Table 2.) Mr. Koller is expected to testify that the USP789 is a requirement for ophthalmic drugs such a VEGF-antagonist solutions intended for intravitreal use. For example, syringe manufacturers were aware that the prefilled syringes needed to have low particulate content that complied with USP 789. (JX-0026C.0003).[25] Thus, the Staff expects the evidence to show that because Sigg

[23] The other disclosed method is the "differential weighing method." ('631 patent, 5:5-9.)

[24] As explained above, Mr. Koller is expected to testify that the recovery rates for the solvent extraction methods known at the time would have been up 95%, *i.e.* the amount identified would be within 5% of the actual amount, which is well with the ±10% that Novartis argues the claim term "about" 1-100 covers. (CX-1184C, Koller Tr., 254:17-255:8; JX-0010C.0002). Moreover, other evidence is expected to show that solvent extraction methods could use "multiple" extractions to fully characterize the amount of silicone in a syringe. (RX-0430.0004.)

[25] The Staff notes that internal Novartis development documents concerning [redacted]

discloses a PFS with ranibizumab, *i.e.* a known VEGF-antagonist solution intended for intravitreal use, it would have obvious to a POSITA that the VEGF-antagonist solution in Sigg must comply with the USP-789 standard.

1(c) … wherein the syringe has a stopper break loose force of less than about 11N.

Sigg does not disclose any particular break loose force. But Boulange discloses several tests of "friction force B" of various syringes. (Boulange at 15:6-8 ("the force required, under static conditions, to break the contact at the contact region 10 between the piston 3 and the container 2").) The Staff expects expert testimony will show that Boulange's "friction force B" is the "break loose force" of the '631 patent.

Table 7 in Boulange discloses the break loose force test results for syringes A and C, which comprised 40 µg of silicone oil on the internal surface and pistons that were not coated with Parylene C. (Boulange, 20:15-17, Table 7.)

[redacted] This further evidence that persons of skill prior to the '631 patent's priority date understood that ophthalmic solutions [redacted] needed to comply with USP 789.

Table 7

		Scenario 1			Scenario 2		
Silicone/internal surface of syringe		4 µg/cm²	4 µg/cm²	4 µg/cm²	50 µg/cm²	50 µg/cm²	50 µg/cm²
Silicone/piston		---	---	---	---	---	---
Force (N)		B	S	F	B	S	F
Piston	A T=0	6.6 (0.3)	6.9 (1.4)	4.0 (1.4)	5.5 (0.5)	1.2 (0.3)	4.0 (2.0)
	A T=1	15.7 (2.9)	5.3 (2.5)	6.1 (4.2)	8.6 (1.1)	1.6 (0.7)	5.6 (4.1)
	B1 T=0	2.1 (0.1)	2.5 (0.3)	2.6 (0.3)	1.9 (0.2)	1.3 (0.3)	2.1 (0.7)
	B1 T=1	3.0 (0.4)	3.4 (0.5)	2.8 (0.8)	2.2 (0.2)	1.4 (0.3)	2.4 (0.6)
	C T=0	3.9 (0.6)	6.6 (2.5)	3.9 (2.5)	4.2 (0.6)	1.0 (0.4)	4.7 (2.9)
	C T=1	14.4 (2.2)	4.8 (2.1)	3.6 (1.1)	5.4 (1.2)	1.3 (0.5)	4.3 (2.8)
	A T=3	17.2 (6.1)	4.3 (2.4)	2.9 (1.2)	10.0 (1.0)	1.5 (0.3)	4.0 (3.0)
	A T=6	20.5 (4.0)	6.1 (3.0)	3.0 (1.0)	15.1 (1.4)	2.5 (1.5)	3.0 (2.0)

(JX-0302.0023, Boulange, Table 7 (annotated))

Additionally, Table 7 discloses the results of syringe B1, which was also siliconized with 40 µg of silicone oil on the internal surface but (unlike A and C) also has a coating of Parylene C on the piston. (*Id.*) In all cases, Table 7 shows that the break loose force at time zero was below 11 N. (*Id.*)

(2) Claims 3 and 22

As explained above, Boulange discloses syringes with 40 µg of silicone oil on the internal surface, and therefore discloses these claims. (Boulange at 20:15-17.)

(3) Claims 4 and 23

The Staff expects the evidence to show that it would have been obvious to use DC365 emulsion, which has a viscosity of about 350 cP. For example, the evidence is expected to show that it was known to use DC 365 as a preferred emulsion for

baked-on siliconization of a PFS, and that DC365 had a viscosity of 350 cP. (JX-0305.0006, Fries 2009; JX-0304.0003 ("The DOW CORNING 365 siliconization emulsion is often used in the baked-on siliconization process").) The '631 patent itself discloses that "typically" either DC360 or DC365 are used for syringe siliconization. ('631 patent, 5:10-13.) The Chan 2012 paper explains:

> There are three types of silicone fluid, or polydimethylsiloxane (PDMS), available for syringe/cartridge lubrication: non-reactive silicone oil (e.g., Dow Corning [DC] 360 Medical Fluid available in five viscosities), non-reactive silicone emulsion (e.g., DC 365 35% Dimethicone NF Emulsion), and reactive (curable) silicone fluid (e.g., DC MDXS-41S9 Medical Grade Dispersion).

(JX-0472.0003.) Thus, a POSITA would have chosen DC 365 out a small number of known options for siliconizing a syringe.

The Staff there expects that the evidence will show it would have been obvious for a POSITA to use a DC365 emulsion, *i.e.* an identified predictable solution within a POSITA's grasp, when siliconizing the Sigg and Boulange combination syringe. *See KSR*, 550 U.S. at 421.

(4) Claims 5 and 6

Like claim element 1(c), claim 5 recites more elements taken from the USP 789 standard, and claim 6 requires the USP 789 standard. For the same reasons identified above with respect to claim 1(c), these limitations would have been obvious over Sigg and Boulange.

(5) Claim 7

Claim 7 requires an "antibody" VEGF antagonist. As explained above, Sigg discloses a PFS containing ranibizumab. The '631 patent identifies ranibizumab as an antibody VEGF antagonist. ('631 patent, 6:30-35.) Thus, the evidence will show that Sigg discloses this limitation.

(6) Claims 11-13

Dependent claims 11, 12 and 13 further require that the VEGF-antagonist is a non-antibody VEGF-antagonist, the non-antibody VEGF-antagonist is aflibercept or conbercept, and the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL, respectively. Neither Sigg nor Boulange expressly disclose this limitation.

But the evidence is expected to show that aflibercept (the active drug in the accused EYLEA PFS) at a concentration of 40 mg/mL was known in the art more than one year prior to the '631 patent priority date. Specifically, the PCT Patent Publication No. WO 2007/149334 to Furfine et al. ("Furfine") discloses a non-antibody VEGF-antagonist aflibercept at a concentration of 40 mg/mL. (JX-0310, ¶¶ 0013-0014, 0059-0060.) The '631 patent discloses that aflibercept was available in the prior art. ('631 patent, 6:38-44.) The Staff believes the evidence will show that it would have been obvious to use different VEGF-antagonist biologic drugs with Sigg and Boulage. (Sigg at 8:6-7 (noting that the terminally sterilized PFS in Sigg is not "drug specific").)

(7) Claim 16

Claim 16 requires a stopper slide force of less than about 11N, which is met by the syringes shown in Table 7 of Boulange. Specifically, expert testimony is expected to show that the "friction force S" and "friction force F" disclosed in Boulange (Boulange at 15:9-11, 15:13-15) are different types of slide forces, measured at different points along the syringe barrel. And Table 7 shows "S" and "F" values for all the syringes that are less than 11N. (Boulange, Table 7.) Mr. Koller is expected to testify that the slide force would increase by approximately 1.3 N if using a VEGF-antagonist such as ranibizumab instead of water. But even with that additional force, the values in Boulange would still be within the limit of claim 16.

(8) Claim 17

Sigg discloses that the PFS is packaged in a blister pack and sterilized with vaporized hydrogen peroxide, *i.e.* H_2O_2, as required by claim 17. (Sigg at 6:26-28, 8:21-24.)

(9) Claim 21

Claim 21 depends from claim 17 and requires "a Sterility Assurance Level of at least 10^{-6}. Sigg discloses that "Sterility" is defined as the "complete absence of microbial life," which includes a "sterility assurance level (SAL)" of 10^{-6}. (Sigg at 7:8-13.) Sigg explains that an embodiment of the disclosed invention is directed to drug products that require "sterility" (*i.e.* including a sterility assurance level of at

least 10^{-6}) and in particular to a "ranibizumab" solution for intravitreal injection. (Sigg at 9:11-14.) Thus, Sigg discloses this claim limitation.

(10) Claims 24 and 25

Claim 24 is directed to a method of treating a patient suffering from of an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising the step of administering an ophthalmic solution to the patient using a pre-filled syringe according to claim 1. Claim 25 depends from claim 24 and is directed to using an initial priming step in which the physician depresses the plunger of the pre-filled syringe to align the predetermined part of the stopper with the priming mark.

As explained above, Sigg discloses ranibizumab, *i.e.* Lucentis. Lucentis was and is used to treat (among other things) wet age-related macular degeneration. (JX-0312.0001, 2010 Lucentis label (under "Indications" identifies "Neovascular (Wet) Age-Related Macular Degeneration (AMD)").) Thus, expert testimony is expected to show that it would have been obvious to use the syringe disclosed in Sigg to treat a patient for wet age-related macular degeneration by administering Lucentis. Moreover, expert testimony is expected to show that it would have been obvious for a physician to perform an initial priming step by aligning the stopper with a priming mark on the syringe. [redacted]

[redacted]

(11) Motivation to combine Sigg and Boulange with a reasonable expectation of success

The Staff believes the evidence will show that a POSITA would have been motivated to combine the terminally sterilized PFS comprising a VEGF-antagonist of Sigg with the low-silicone and low break loose/gliding force syringe of Boulange, and would have had a reasonable expectation of success in doing so.

(a) General knowledge of persons of skill in the art

First, the evidence will show that it was known in the art that prefilled syringes are typically siliconized. (*See e.g.* '631 patent, 4:48-50 ("It is typical to siliconise the syringe in order to allow ease of use, i.e. to apply silicone oil to the inside of the barrel, which decreases the force required to move the stopper"); JX-0491.0004 ("As performed for vials and stoppers, prefilled syringe components require preparation before use, involving washing, siliconization and sterilization"); RX-0995.0001; JX-0305 ("Functionality of [prefilled syringes] (viable activation and gliding forces of the plunger) is accomplished by siliconization"); RX-0486.0003 ("Silicone oil is applied to coat the barrel plunger and needle exterior"); RX-0967.0004 ("Siliconisation of the glass barrel is one of the key process steps, as silicone is the lubricant required to allow movement of the rubber plunger through the syringe forcing the drug out of the container to finalise the injection").)

It was also well known in the art that when using a silicone oil coating on a syringe, it was important to minimize the amount of silicone oil injected into a human being. (JX-0338.0065.) This was particularly true with intravitreal injections, where it was known that silicone oil could be harmful to the human eye, *e.g.* by causing "floaters" or increased intraocular pressure. ('631 patent, 4:53-55; JX-0311.0001; CX-0292.0005-6.) By at least 2010, persons of skill were raising concerns about the silicone oil in the Macugen PFS being injected into patients' eyes. (RX-0995.0001.)

Moreover, the evidence and expert testimony is expected to show that it was known that excess silicone oil could interact negatively with the drug formulations in a syringe, and in particular with protein therapies such as the VEGF-antagonists at issue here. (JX-0304.0004; JX-0298 (noting that reducing free silicone levels by using baked-on silicone was "a clear benefit for silicone sensitive drugs"); JX-0306.0004; RX-0578; RX-0558; JX-0485.) A 2007 article explains that in response to concerns over the impact of silicone oil on certain drugs, "companies are baking on the silicone and still others are working to reduce the amount of silicone in the barrels to the least amount possible to still allow the plunger to move." (RX-0475.0003; *see also* RX-0473 ("Although the quantity of silicone oil on the glass is generally kept to the lowest amount possible the product is in contact with it during storage").)

The Staff also notes that the evidence will show that some of the motivation for Novartis to develop a PFS with low amounts of silicone came originally from

[redacted] In the Staff's view, that evidence is consistent with the publicly available documents showing that persons of skill were generally aware that reducing the amount of silicone oil in intravitreal injections was desirable.

Second, the Staff believes that expert testimony and other evidence will show that it was well known that low break loose and gliding forces were important for syringes used for intravitreal injections. Injections into the eye require "[e]xtreme care and precise technique" in order "to minimize or prevent damage to the eye." (JX-0338.0036.) The '631 patent explains in the "Background Art" section that a syringe must "remain easy to use, in that the force required to depress the plunger to administer the medicament must not be too high." ('631 patent, 1: 37-40.) The '631 patent also discloses that break loose and slide forces for prefilled syringes known in the prior art were "typically in the region of less than 20N." ('631 patent, 5:35-37.) For example, Dr. Arno Fries of Gerresheimer Group disclosed in a 2009 article that by using "low levels of lubricant quantity," syringe gliding forces in the range of 5 to 10N could be achieved and were sufficient for "syringe functionality." (JX-0305.0007.) Similarly, the Shah article explains that an advantage of baked-on silicone technology is that "initial force required to inject using prefilled syringes with baked on silicone remains consistently low before and after storage." (JX-0298.0006.) Dr. Thomas Schönknecht made a similar point in a 2005 article, explaining that with baked-on siliconization, "Lubrication is maintained so that the initial force required to inject using prefilled syringes with baked on silicone

remains consistently low before and after storage."[26] (JX-0306.0004.) A 2006 article by David Overcashier[27] and others at Genentech reported on break loose and glide force tests run on "typical" prefilled syringes with "film-coated" and uncoated plunger-stoppers.[28] (JX-0491.0004, 0006.) The data showed that such prior art syringes had a break loose force of between 5 and 8N, and gliding forces between 9-10N. (*Id.*)

Thus, the Staff believes that the evidence will show that a POSITA designing a PFS for intravitreal injections would have been motivated to minimize the break loose and gliding forces.

(b) Sigg and Boulange

In light of the motivations identified above, the Staff believes the evidence will show that a POSITA would been motivated to combine Sigg and Boulange and would have had a reasonable chance of success at doing so.

First, Sigg does not disclose a siliconized syringe, but the evidence above will show that a POSITA understood that a syringe for intravitreal injection (such as

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[26] *See also* RX-0569.0036, Oct. 2005 presentation to PDA Conference, "The Universe of the Pre-filled Syringes" by Dr. Thomas Schönknecht of Gerresheimer (chart showing break loose and glide forces under 10N on slide describing "optimal" siliconization of a syringe).

[27] As noted below, Mr. Overcashier was deposed in this case regarding issues related to Genentech. (JX-0412C, Overcashier Tr.)

[28] The articles notes elsewhere that prefilled syringes are required to be siliconized. (JX-0491.0004 ("As performed for vials and stoppers, prefilled syringe components require preparation before use, involving washing, siliconization and sterilization.").)

Sigg) effectively requires some kind of lubrication to perform appropriately, and silicone was the standard option. (RX-0995.0001; JX-0305 ("Functionality of [prefilled syringes] (viable activation and gliding forces of the plunger) is accomplished by siliconization").) Dr. Sigg testified that at least by 2007, he was aware that zero silicone on a PFS resulted in forces that were too high. (JX-0416C, Sigg Tr. at 222:20-223:11.) Thus, the Staff believes the evidence will show that a POSITA would have been motivated to siliconize the PFS disclosed by Sigg.

Second, the evidence will show that a POSITA using Sigg to design a terminally sterilized PFS for intravitreal injection of a VEGF-antagonist would have been motivated to use a low silicone syringe to minimize the amount of silicone in the syringe. As explained above, the potential harmful effects of silicone oil on a sensitive drug such as the ranibizumab disclosed in Sigg were well known, and a POSITA would be motivated to use the 40 µg of baked-on silicone oil syringe in Boulange to avoid those problems. Indeed, Boulange itself provides such motivation by explaining the importance of "limit[ing the risk of interaction between a lubricant for example silicone oil and the therapeutic molecules potentially stored in the container of the medical device prior to delivery to a patient." (Boulange, 6:26-29.) Moreover, expert testimony is expected to show that minimizing the amount of silicone oil in the syringe by using Boulange would be important to comply with requirements of USP 789 by minimizing particulate matter in the syringe. Thus, there would have been regulatory pressure to keep silicone amounts low.

Third, the evidence above shows that a POSITA would have motivated to keep the break loose and gliding forces of the Sigg PFS low to maintain syringe functionality. (JX-0305.0007.) Boulange discloses break loose and glide forces well below both the claimed 11N and below the 20N upper limit disclosed in the specification of the '631 patent. A POSITA would therefore be motivated to use the Boulange syringes with the Sigg PFS to take advantage of Boulange's low break loose and gliding forces.

Fourth, the Staff believes the evidence will show that a POSITA would have a reasonable chance of success in implementing the terminally sterilized Sigg PFS with the Boulange syringe. For example, the evidence is expected to show that Macugen PFS used a [redacted] and was terminally sterilized [redacted] [redacted] (JX-0145C.0012; JX-0004C.0084, 0230.) Thus, devices were already known in the art that taught how to terminally sterilize a PFS. The Staff therefore expects the evidence will show that a POSITA would need to perform only routine optimization to terminally sterilized the Sigg PFS in a Boulange syringe.

Finally, the Staff notes that Boulange, [redacted], is a Becton Dickinson patent. BD is a major manufacturer of syringes (both at the time of the '631 patent priority date and today). (JX-0272C.0001-9.) And more specifically, before the priority date of the '631 patent, BD was one of the world's largest makers of prefilled syringes. (RX-0496.0003 (2003 article explaining that BD "manufactures most of the prefillable syringes used worldwide").) Similarly, [redacted]

[redacted] (CX-0778C, ¶ 7.) In the Staff's view, it would be common sense for a POSITA implementing the Sigg PFS to look for a syringe developed or sold by one of the world's major prefilled syringe manufacturers.

(c) Novartis's position

Novartis argues that a POSITA would not start with Sigg because "Sigg does not enable a syringe that can be terminally sterilized," and identifies a number of reasons why Sigg would allegedly not have enabled a POSITA to terminally sterilize a syringe. (CPreBr. at 102-106.) But even if factually true, that argument is legally irrelevant. "Under an obviousness analysis, a reference need not work to qualify as prior art; it qualifies as prior art, regardless, for whatever is disclosed therein." *See Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1302 (Fed. Cir. 2010); *see also ABT Sys., LLC v. Emerson Elec. Co.*, 797 F.3d 1350, 1360 n. 2 (Fed. Cir. 2015) (internal citations and quotation marks omitted); *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed.Cir.1989) ("an inoperative device ... is prior art for all that it teaches,").

Similarly, Novartis's argument that "Sigg does not identify any suitable combinations of components that create a tight enough seal to prevent VHP ingress, or provide instructions or guidance regarding the design of components useful for that application," (CPreBr. at 104) is also irrelevant because the claims do not require any of those elements either. Claim 1 simply requires a "terminally sterilized syringe" and the standard components of such a syringe ("a glass body

forming a barrel, a stopper and a plunger"). The '631 patent discloses but does not claim a structure that Novartis implies enables terminal sterilization of a PFS. ('631 patent at Figs. 1-4 and accompanying text; CPreBr. at 103 ("[redacted].") But unclaimed features cannot be used to distinguish a patent over the prior art. *See Mettler-Toledo*,, 671 F.3d at 1298; *Ormco*,, 463 F.3d at 1308. Thus, Sigg discloses a terminally sterilized syringe to the same extent that such a syringe is claimed by the '631 patent, and therefore renders the claim obvious as explained above. Moreover, Macugen PFS disclosed a syringe design for a terminally sterilized and siliconized pre-filled syringe for intravitreal injection. (See Section IV.D.1.h.1.)

Novartis also argues that a POSITA would not have been motivated to reduce silicone oil levels both generally and to the specific amount disclosed in Boulange. (CPreBr. at 107-111.) The Staff believes the evidence identified above contradicts the first point, and any concern about lowering the silicone amount so much that "mechanical failure" occurred (CPreBr. at 108) is belied by Boulange's disclosure of test results showing that a syringe with 40 µg of baked-on silicone oil achieved the appropriate forces without suffering "mechanical failure." (Boulange, Table 7.) In other words, Boulange's disclosure is proof that a POSITA would know that silicone oil could be reduced below 100 µg while maintaining appropriately low break loose and glide forces. As to the second point, that a POSITA would not pick the

specifically low numbers identified in Boulange, the evidence shows that a POSITA would want to minimize the amount of silicone while still maintaining low break loose and glide forces. Boulange accomplishes that goal and that is why a POSITA would combine it with Sigg.

Finally, Novartis argues that a POSITA would not have used Boulange with Sigg because of Boulange's use of Parylene C in some embodiments. (CPreBr. at 111-126.) The Staff disagrees with this argument for two reasons.

First, Boulange itself discloses that Parylene C is appropriate for use in a syringe and the use of Parylene C allows a reduction in the use of silicone oil that could interfere with a therapeutic molecule. (Boulage, 8:26-29 ("[T]he medical device of the invention allows to limit the risk of interaction between a lubricant for example silicone oil and the therapeutic molecules potentially stored in the container of the medical device prior to delivery to a patient").) Whether a device using Parylene C would ultimately be approved by the FDA is not particularly relevant. *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1192 (Fed. Cir. 2019) (upholding the district court's finding that "the standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA") (internal quotation marks omitted). And the claims of the '631 patent do not require FDA approval, nor do they forbid the use of coatings on the plunger (such as the Parylene C in Boulange).

Evidence, including testimony from Mr. Koller, is also expected to show that the use of Parylene C on a piston would be acceptable for intravitreal syringes and

compatible with sterilization techniques disclosed by Sigg. (JX-0457.0002 ("Parylene has been used in a wide range of medical device and component applications since the 1970s. These include catheters and mandrels, stents, needles, cannulae, cardiac assist devices, prosthetics, and electronic circuitry"); JX-0038.0010; JX-0299.0044 ("Parylene is widely applied on syringes to make their use easier and more precise").)

Novartis points to a study by Kaminska as evidence that Parylene C would not be suitable to use with a VEGF-antagonist (CPreBr. at 116), but Kaminska studied "blood plasma proteins, platelets, endothelial cells, and bacterial biofilm," not VEGF-antagonists. (CX-1260.0001.) Nothing in Kaminska suggests that Parylene C should not be used with VEGF-antagonists such as the ranibizumab disclosed in Sigg. Moreover, Kaminska concludes that "[t]he results presented strongly support the thesis that parylene C is worth considering for biomedical use." (*Id.* 0006.) This is consistent with other prior art evidence explaining that "[b]ecause of its excellent barrier properties, Parylene C is often the first choice for protection of pharmaceutical containers, syringes and vials." (JX-0299.0045.) The evidence will show that the makers of Parylene advertised it specifically for use with syringes:

(JX-0299.0046, October 2012 advertisement for Parylene)

Thus, the Staff believes the evidence will show that a POSITA would not hesitate to use the Parylene-C-coated-piston prefilled syringe in Boulange with the prefilled syringe of Sigg.

Second, Boulange also discloses syringes without Parylene C that are siliconized with only 40 µg of silicone oil (*i.e.* A and C in Table 7). Novartis argues that Boulange teaches away from using such syringes because it states that they were "markedly inferior" than the Parylene C syringe and were not "acceptable for a medical device."[29] (CPreBr. at 125.) The Staff disagrees. The fact that Boulange

[29] Novartis also points to the fact that the Boulange break loose force and glide forces were above the claim limitations after one month of storage for the non-Parylene C syringes (CPreBr. at 114.) But Novartis has waived any argument that the time when the break loose force or glide force is measured has any bearing on the scope of the claims. (EDIS Doc. ID 726358, Novartis's Responsive *Markman* Brief, at 10 ("If an accused device reads on the claims at the time of a potential infringing act (e.g., use, sale, importation, etc.), it infringes; the possibility that the device conditions could later change over time does not create ambiguity as to claim scope.").)

preferred the Parylene C coating over the syringes lacking such a coating is not, in the Staff's view, evidence that Boulange teaches away. *Dome Pat. L.P. v. Lee*, 799 F.3d 1372, 1381 (Fed. Cir. 2015) ("[J]ust because 'better alternatives' may exist in the prior art 'does not mean that an inferior combination is inapt for obviousness purposes.'"); *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344, 1355-56 (Fed. Cir. 2012) (prior art did not teach away when it merely characterized the alleged inventive feature as being a "second-best choice"). The Federal Circuit has also made clear that "our case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention." *Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019) (internal quotation marks omitted). That the Parylene C-free syringe may not have been the preferred embodiment in Boulange does not mean a POSITA would ignore it.

Moreover, to the extent Boulange's statement that the non-Parylene C syringes resulted in forces that were not "acceptable for a medical device" can be taken as a teaching away, the Staff believes the evidence will show that the prior art as a whole disclosed that the forces disclosed in Boulange were acceptable for a pre-filled syringe. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013) (holding that district court erred by not considering whether prior art "as a whole" taught away). In particular, the '631 patent teaches that forces under 20N were considered acceptable, and Fries teaches that forces between 5 and 10N were acceptable. ('631 patent, 5:35-37; JX-0305.0007; RX-0569.0036.) Thus, a POSITA

would have understood from the prior art "as a whole" that the break loose and glide forces disclosed in Boulange for the non-Parylene C were acceptable for a prefilled syringe.

c. Sigg in view of [redacted]

(1) Claim 1

1[preamble] A pre-filled, terminally sterilized syringe for intravitreal injection, the syringe comprising a glass body forming a barrel, a stopper and a plunger and containing an ophthalmic solution which comprises a VEGF-antagonist, wherein:

Sigg discloses this limitation. (*See supra* at p. 45.)

Additionally, the [redacted] was a glass syringe with a barrel, stopper, and a plunger. (JX-0009C.0001; JX-0007C.0002.) Expert testimony is also expected to show that the [redacted] syringes were a well-known product-line of prefilled syringes sold by [redacted] (RX-0496.0003.)

1(a) the syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml,

Sigg discloses this limitation. (*See supra* at p. 47.) Additionally, the [redacted] was a 1 ml syringe. (JX-0007C.0002.)

1(b) the syringe barrel comprises from about 1 µg to 100 µg silicone oil,

[redacted] comprised between [redacted] and [redacted] µg of silicone oil:

[redacted]

(JX-0007.0002 (annotated))

(JX-0007C.0003)

The 2010 slide deck about [redacted] explains that the [redacted] (JX-0007.0003.) The Staff expects that Mr. Koller will testify that [redacted] The 2010 slide deck also explains with respect to the [redacted] (JX-0007C.0010.)

Novartis contends that the evidence is unclear as to whether any [redacted] syringe allegedly sold in the U.S. actually had the properties disclosed in the 2010 slide deck. (CPreBr. at 137-38.) Novartis relies on the [redacted] (JX-0010C) for this contention. But the letter does was written (and sent) by Mr. [redacted] and

Mr. [redacted] asserted in his declaration that the slides at JX-0007C.0002-0006 reflected the amount of silicone oil in syringes that were on sale in the U.S. in 2011. Nothing in the text of the letter contradicts that declaration, and as explained above, the Staff is not aware of any reason to doubt Mr. [redacted] veracity or credibility. (*See supra* at 38-40.)

Novartis also appears to argue that the slide deck's reference to [redacted] means the actual amounts of silicone were likely to be higher than what was disclosed. (CPreBr. at 138.) For the same reasons expressed above with respect to Boulange, the Staff disagrees with that argument. (*See supra* at 49.)

1(c) the VEGF antagonist solution comprises no more than 2 particles >50 µm in diameter per ml and …

The Staff expects the evidence will show this limitation would have been obvious in light of Sigg and the USP 789 standard. (*See supra* at 50.)

1(c) … wherein the syringe has a stopper break loose force of less than about 11N.

The [redacted] had '[redacted] forces of less than "about 11N" (identified in the charts below for each tested syringe as the [redacted]

(JX-0007C.0004)

Syringes [redacted] all had a measured maximum break loose forces less than 11N, while the [redacted] syringe, which corresponds to Syringe [redacted] ([redacted] µg of silicone oil), had a maximum break loose force of [redacted] N, which is less than "about" 11N. (JX-0007C.0004) Moreover, every syringe had an average break loose force less than 11N.[30]

(2) Claims 3 and 22

As explained above, [redacted] comprised [redacted] µg of silicone oil. (JX-0007C.0002-3)

[30] [redacted]

(3) Claims 4 and 23

The Staff expects the evidence to show that it would have been obvious to use a DC365 emulsion, which has a viscosity of about 350 cP. (*See supra* at 52.)

(4) Claims 5 and 6

Like claim element 1(c), claim 5 recites more elements taken from the USP 789 standard, and claim 6 requires the USP 789 standard. For the same reasons identified above with respect to claim 1(c), these limitations would have been obvious over Sigg and [redacted].

(5) Claim 7

Sigg discloses this limitation. (*See supra* at 54.)

(6) Claims 11-13

These claims would have been obvious over Sigg. (*See supra* at 54.)

(7) Claim 16

[redacted] had a maximum glide force of less than 11N. Specifically, the [redacted] syringe [redacted] and syringes [redacted], shown in the 2010 slide deck all had maximum and average glide forces less than 11N. (JX-0007C.004.)

Mr. Koller is expected to testify that the slide force would increase by approximately 1.3 N if using a VEGF-antagonist such as ranibizumab instead of water. But even that additional force would still be within the limit of claim 16.

(8) Claim 17

Sigg discloses this limitation. (*See supra* at 55.)

(9) Claim 21

Sigg discloses this limitation. (*See supra* at 55.)

(10) Claims 24 and 25

As explained above, these claims would have been obvious in light of Sigg and the prior art. (*See supra* at 56.)

(11) Motivation to combine Sigg and [redacted] with a reasonable expectation of success

For the reasons explained above, the Staff believes the evidence will show that a POSITA would have been motivated to use a low silicone oil syringe with low break loose and glide forces with the terminally sterilized PFS of Sigg. (*See supra* at Section IV.D.1.b.15(a)-(b)). And [redacted] offered those properties and was on sale in the U.S. from [redacted]. (JX-0007C.0006 ([redacted]orces).) It would have been common sense for a POSITA to investigate using a prefilled syringe from [redacted]

The Staff also believes the evidence will show that a POSITA would have a reasonable chance of success in implementing the terminally sterilized Sigg PFS with the [redacted]. For example, the evidence is expected to show that Macugen PFS used a [redacted] syringe and was terminally sterilized using [redacted]bs. (JX-0004C.0032, 0058, 0084, 0224-0236.) In other words, the prior art already disclosed the mechanical structure of a PFS that could be terminally sterilized.

(JX-0004C.0058 (annotated))

(JX-0004C.0230 & 0236 ( ))

Thus, devices were already known in the art that achieved a terminally sterilized PFS.[31] The Staff therefore expects the evidence will show that a POSITA

[31] The Staff notes that the '631 patent discloses but does not claim a structure that allegedly enables terminal sterilization of a PFS. ('631 patent at Figs. 1-4 and accompanying text.) But unclaimed features cannot be used to distinguish a patent over the prior art. See *Mettler-Toledo*, 671 F.3d at 1298; *Ormco*, 463 F.3d at 1308.

would need to perform only routine optimization to terminally sterilize the Sigg PFS in a [redacted] syringe.

Novartis argues that the [redacted] (JX-0010C) and slides (JX-0007C) teach away from using a syringe with less than 100 µg of silicone oil. (CPreBr. at 138-141.) The Staff disagrees because that argument misconstrues the invalidity position; the claims of the '631 patent are not obvious over the [redacted] and slide deck, rather, the claims are obvious over a device that was on sale before the '631 patent's critical date. And the [redacted]etter (JX-0010C) and slides (JX-0007C) (along with the invoice, price quote, and Mr. [redacted] declaration) are being used to prove (1) the properties of that device, and (2) the on-sale status of that device. Thus, the Staff does not believe that any disclosure in the confidential letter or slide deck could teach a POSITA anything, let alone teach away from using less than 100 µg of silicone oil on a syringe.

Novartis also claims the slide deck shows that the [redacted] was being marketed for [redacted] (CPreBr. at 141.) But as noted above, Macugen PFS used a [redacted] syringe, which shows that [redacted] syringes were not only marketed and used for [redacted] but were being marketed and used for intravitreal injections. In any event, if the break loose and slide forces achieved by the [redacted] syringes were appropriate for intravitreal injection, Novartis does not put forward any evidence that a POSITA would ignore such syringes, particularly since the [redacted]. *See KSR*, 550 U.S. at 401

("When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another").

Novartis also argues that Sigg and [redacted] do not disclose the specific syringe components necessary to implement a terminally sterilized PFS. (CPreBr. at 142-142.) But as explained above, the '631 patent does not claim any specialized components of a syringe to enable terminal sterilization. (*See supra* at 63.) Moreover, Macugen PFS disclosed a syringe design for a terminally sterilized and siliconized pre-filled syringe for intravitreal injection. (*See* Section IV.D.1.h.1.)

d. Lam in view of Boulange or [redacted]

(1) Claim 1

1[preamble] A pre-filled, terminally sterilized syringe for intravitreal injection, the syringe comprising a glass body forming a barrel, a stopper and a plunger and containing an ophthalmic solution which comprises a VEGF-antagonist, wherein:

Lam discloses a terminally sterilized PFS for intravitreal injection. (Lam, at 2:7-17, 22-24, 29-33; 11:30-31 ("In some embodiments the pharmaceutical composition is designed for intraocular injection").) Lam discloses that the PFS may contain a VEGF-antagonist, and in particular, ranibizumab (*i.e.* Lucentis). (*Id.* at 2:23-24.) Lam also discloses that the syringe may be made of glass. (Lam at 2:29-30, claims 20 and 21.)

As explained above, Boulange and [redacted] both disclose pre-filled glass syringes.

1(a) the syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml,

Expert testimony is expected to show that it would have been obvious to use a 0.5 ml – 1 ml syringe for an intravitreal injection (such as the ranibizumab disclosed by Lam) given the small amount of drug product injected. (JX-0338.0017.) Moreover, Lam discloses using another VEGF-antagonist, Macugen (Lam at 11:9-11), and it was known in the art that Macguen was sold in a 1 ml PFS. (JX-0322.0009.)

As explained above, Boulange and [redacted] both disclose pre-filled glass syringes with a nominal fill volume of 1 ml.

1(b) the syringe barrel comprises from about 1 µg to 100 µg silicone oil,

As explained above, Boulange and [redacted] both disclose pre-filled glass syringes with between 1 and 100 µg of silicone oil.

1(c) the VEGF antagonist solution comprises no more than 2 particles >50 µm in diameter per ml and …

Lam discloses a PFS used for the intravitreal injection of ranibizumab. (Lam, at 2:7-17, 22-24, 29-33.) For the same reasons as explained with respect to Sigg, the evidence will show this limitation would have been obvious in light of Lam and the USP 789 standard. (*See supra* at 50.)

1(c) … wherein the syringe has a stopper break loose force of less than about 11N.

As explained above, Boulange and [redacted] both disclose pre-filled glass syringes with stopper break loose forces less than 11N.

(2) Claims 3 and 22

As explained above, Boulange and [redacted] both disclose these claims.

(3) Claims 4 and 23

The Staff expects the evidence to show that it would have been obvious to use a DC365 emulsion, which has a viscosity of about 350 cP. (*See supra* at 52.)

(4) Claims 5 and 6

Like claim element 1(c), claim 5 recites more elements taken from the USP 789 standard, and claim 6 requires the USP 789 standard itself. For the same reasons identified above with respect to claim 1(c), these limitations would have been obvious over Lam and [redacted] or Boulange.

(5) Claim 7

Claim 7 requires an "antibody" VEGF antagonist. As explained above, Lam discloses a PFS containing ranibizumab. The '631 patent identifies ranibizumab as an antibody VEGF antagonist. ('631 patent, 6:30-35.) Thus, the evidence will show that Lam discloses this limitation.

(6) Claim 11

Dependent claim 11 requires that the VEGF-antagonist is a non-antibody VEGF-antagonist. Lam discloses the use of pegaptanib (*i.e.* Macugen) which is a non-antibody VEGF-antagonist. (Lam at 11:9-11.)

(1) Claims 12-13

Dependent claims 12 and 13 further require a non-antibody VEGF-antagonist that is aflibercept or conbercept, and that the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL, respectively. Neither Lam nor Boulange[redacted] expressly discloses aflibercept. However, the evidence is expected to show that aflibercept (the active drug in the accused EYLEA PFS) at a

concentration of 40 mg/mL was known in the art more than one year prior to the '631 patent priority date. Specifically, the PCT Patent Publication No. WO 2007/149334 to Furfine et al. ("Furfine") discloses the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL. (JX-0310, ¶¶ 0013-0014, 0059-0060.) The '631 patent discloses that aflibercept was available in the prior art. ('631 patent, 6:38-44.) The Staff believes the evidence will show that it would have been obvious to use different VEGF-antagonist biologic drugs with Lam and Boulage. (Lam, 11:12-13 ("As used herein a pharmaceutical composition is a solution comprising a compound which is suitable for administration to a subject"); *id.* at 12:31-32 ("The methods of the invention are typically used to sterilize objects containing pharmaceutical formulations").)

(2) Claim 16

As explained above, Boulange and [redacted] both disclose this claim.

(3) Claim 17

Lam discloses a PFS in a TYVEK blister package that is terminally sterilized with EtO. (Lam at 2:29-33.) The Staff expects that expert testimony will show that TYVEK was a commonly used material for blister packs used to package prefilled syringes. (RX-0593.0003 ("Du Pont Tyvek spunbonded olefin is intended for packaging of terminally sterilized medical devices").)

(4) Claim 21

Lam discloses that "the surface of an object is sterilized when the amount of at least one biological contaminant present on the surface of the object being treated

according to the present invention is reduced following the treatment. Typically, the amount is reduced by at least one log (*i.e.* by at least 10-fold). In some embodiments of the invention the amount is reduced by 2 logs 3 logs 4 logs 5 logs or 6 logs." (Lam at 4:3-7.) The Staff expects expert testimony to explain that a "6 logs" reduction in biological contaminants is equivalent to a sterility assurance level of 10^{-6}.

(5) Claims 24 and 25

For the same reasons explained above with respect to Sigg (which, like Lam, discloses ranibizumab), these claims would have been obvious in light of Lam and the prior art. (*See supra* at 56.)

(6) Motivation to combine Lam and Boulange or [redacted] ith a reasonable expectation of success

For the same reasons expressed above with respect to Sigg and Boulange, and Sigg and [redacted], the Staff believes the evidence will show that a POSITA would be motivated to combine Lam's terminally sterilized PFS containing a VEGF-antagonist with a low silicone, low break loose and glide force syringe. (*See* Sections IV.D.1.b.14 & IV.D.1.c.15.) Boulange or [redacted] both provide such a syringe. And for the same reasons expressed above, the Staff believes a POSITA would be successful in combining Lam with Boulange or [redacted] for the same reasons expressed with respect to Sigg. (*Id.*)

Novartis makes roughly the same arguments with respect to the Lam combinations as the Sigg combinations, *i.e.* that Lam does not disclose the components necessary to build a terminally sterilized pre-filled syringe. (CPreBr. at

144-147.) But as explained above, the '631 patent does not claim those features either, so the lack of those features in Lam cannot save the claims. (*See supra* at 63.) Moreover, Macugen PFS disclosed a syringe design for a terminally sterilized and siliconized pre-filled syringe for intravitreal injection. (*See* Section IV.D.1.h.1.)

Novartis also raises the issue that Lam's assignee, Genentech, [redacted] (CPreBr. at 148.) But again, [redacted] because Lam discloses exactly what the '631 patent claims: a terminally sterilized PFS. To the extent specialized syringe components are necessary to enable a terminally sterilized syringe to be combined with a low silicone oil syringe, such components are not claimed by the '631 patent and thus cannot differentiate the '631 patent over the prior art.

e. Macugen PFS in View of Boulange or [redacted]

(1) Claim 1

1[preamble] A pre-filled, terminally sterilized syringe for intravitreal injection, the syringe comprising a glass body forming a barrel, a stopper and a plunger and containing an ophthalmic solution which comprises a VEGF-antagonist, wherein:

The evidence is expected to show that Macugen PFS is a PFS for intravitreal injection. (JX-0303.0001 ("Macugen® pegaptanib sodium injection is a sterile aqueous solution containing pegaptanib sodium for intravitreous injection. Macugen is supplied in a single dose pre filled syringe…").) Macugen PFS used a glass syringe barrel comprising a barrel, stopper, and a plunger. (*Id.* at 0002, 0008-

9.) The active drug substance in Macugen PFS was pegaptanib, which the Macugen label describes as "a selective vascular endothelial growth factor VEGF antagonist." (*Id.* at 0002.) As explained above, Boulange and [redacted] both disclose pre-filled glass syringes as well.

The Staff further expects the evidence to show that Macugen PFS was terminally sterilized as of 2008. The evidence will show that a 2004 FDA-approved Macugen label explained in the "How Supplied" section that "Macugen pegaptanib sodium injection is supplied in a single use 1 mL glass syringe." (JX-0322.0009.) [redacted]

[redacted]

A publicly available label for Macugen in 2008 contained the new label text in the "How Supplied" section. (JX-0303.0008 ("Macugen pegaptanib sodium injection is supplied in a sterile foil pouch as a single-use glass syringe").) [redacted], which in turn shows that by 2008 Macugen was terminally sterilized. [redacted]. (RX-0972C.0002; JX-0083C.0019; RX-0981C.0015; JX-0416C, Sigg Tr. at 36:5-38:7; JX-0415C, Roettele Tr. at 34:4-39:18, 106:2-109:12.)

Novartis argues that the [redacted]. (CPreBr. at 152-53.) In the Staff's view, however, [redacted]

[redacted]

Novartis also argues that there is no evidence that [redacted] (CPreBr. at 153.) But Novartis does not dispute that JX-0303 accurately discloses the updated Macugen PFS label from 2008, which contains the new "sterile foil pouch" language. (JX-0303.0008.) [redacted]

The more reasonable interpretation of the evidence is that [redacted].

1(a) the syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml,

Macugen PFS used a 1 ml glass syringe. (JX-0322.0009; JX-0004C.0225; JX-0303.0010.)

As explained above, Boulange and [redacted] both disclose pre-filled glass syringes with a nominal fill volume of 1 ml.

1(b) the syringe barrel comprises from about 1 µg to 100 µg silicone oil,

The Macugen PFS syringe was siliconized using [redacted]. (JX-0004C.0225.) But the evidence is expected to show that Macugen PFS used [redacted]. (JX-0006C.0009.)

As explained above, however, Boulange and [redacted] both disclose pre-filled glass syringes with between 1 and 100 µg of silicone oil. Expert testimony is expected to calculate that using the rate of silicone application of 4 µg/cm^2 disclosed in Boulange with the syringe disclosed by the Macugen PFS would result in an internal coating of approximately 43 µg.

1(c) the VEGF antagonist solution comprises no more than 2 particles >50 µm in diameter per ml and …

[redacted]

1(c) … wherein the syringe has a stopper break loose force of less than about 11N.

As explained above, Boulange and [redacted] both disclose pre-filled glass syringes with stopper break loose forces less than 11N.

(2) Claims 3 and 22

As explained above, Boulange and [redacted] both disclose these claims.

(3) Claims 4 and 23

The Staff expects the evidence to show that it would have been obvious to use a DC365 emulsion, which has a viscosity of about 350 cP. (*See supra* at 52.)

(4) Claims 5 and 6

Like claim element 1(c), claim 5 recites more elements taken from the USP 789 standard, and claim 6 requires the USP 789 standard itself. For the same reasons identified above with respect to claim 1(c), these limitations are disclosed by Macugen PFS.

(5) Claim 7

Macugen PFS discloses pegaptanib, which is a non-antibody VEGF-antagonist. However, the evidence is expected to show that antibody VEGF antagonists such as ranibizumab were known in the art more than one year prior to the '631 patent priority date. For example, Sigg discloses ranibizumab. (JX-0301, 9:11-14; JX-0517.) The Staff believes the evidence will show that it would have been obvious to use different VEGF-antagonist biologic drugs with Macugen PFS and Boulange or [redacted], to take advantage of the combination of a terminally sterilized PFS with low silicone oil and low break loose forces.

(6) Claim 11

Dependent claim 11 requires that the VEGF-antagonist is a non-antibody VEGF-antagonist. Macugen PFS discloses the use of pegaptanib, which is a non-antibody VEGF-antagonist. (JX-0303.0002.)

(7) Claims 12-13

Dependent claims 12 and 13 further require a non-antibody VEGF-antagonist that is aflibercept or conbercept, and that the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL, respectively. Neither Macugen PFS nor Boulange/[redacted] expressly discloses aflibercept. But the evidence is expected to show that aflibercept (the active drug in the accused EYLEA PFS) at a concentration of 40 mg/mL was known in the art more than one year prior to the '631 patent priority date. Specifically, Furfine discloses the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL. (JX-0310, ¶¶ 0013-0014, 0059-0060.) The '631 patent discloses that aflibercept was available in the prior art. ('631 patent, 6:38-44.) The Staff believes the evidence will show that it would have been obvious to use different VEGF-antagonist biologic drugs with Macugen PFS and Boulange or [redacted], to take advantage of the combination of a terminally sterilized PFS with low silicone oil and low break loose forces.

(8) Claim 16

As explained above, Boulange and [redacted] both disclose this claim.

(9) Claim 17

Macugen PFS was provided in a sterile foil pouch, not a blister pack. But in the Staff's view, the evidence will show that it would have been a mere design choice for a POSITA to select a blister pack from among a finite number of well-known packaging systems. And both Sigg and Lam disclose blister packs suitable for terminal sterilization. (Sigg, at 6:26-28, 8:8-13; Lam at 2:29-33.) Thus, a

POSITA would have known that the design choice between a foil pouch or a blister pack would have a predictable result based on the known results of Sigg and Lam.

(10) Claim 21

[redacted]

(11) Claims 24 and 25

The Staff expects the evidence to show that Macguen PFS discloses both of these claims. First, the Macugen label indicates that it "is indicated for the treatment of neovascular wet age related macular degeneration." (JX-0303.0005; JX-0322.0006.)

Second, the "Dosage and Administration" instructions indicate a physician should perform an initial priming step: "[D]epress the plunger to eliminate all the bubbles and to expel the excess drug so that the top edge of the 3rd rib on the plunger stopper aligns with the preprinted black dosing line." (JX-0303.0007.)

(12) Motivation to combine Macugen PFS and Boulange or [redacted] with a reasonable expectation of success

The Staff believes the evidence will show that a POSITA would have been motivated to modify the Macugen PFS to use the low silicone oil and low break loose force syringes of Boulange or [redacted]. As an initial matter, the same background pressures identified with respect to Sigg (*i.e.* a desire to minimize

silicone oil while maintaining low break loose forces) apply to this combination as well. (*See* Sections IV.D.1.b.14 & IV.D.1.c.15.)

Additionally, a POSITA would have had specific reason to improve the Macugen PFS. There is some indication that persons of skill were concerned that use of Macugen PFS could lead to excessive silicone oil being injected into the eye. (RX-0423.) Expert testimony is expected to show that Macugen PFS used oily siliconization. It was known that a benefit of using baked-on siliconization as compared to oil siliconization was that the baking process reduced the level of free silicone in the syringe. (JX-0298.0004 ("Baked Silicone: Binding the silicone to the glass barrel through a proprietary technology reduces the level of free silicone. This is a clear benefit for silicone sensitive drugs"); JX-0338.0330 ("Recent developments to minimize free silicone include baking silicone at high heat onto the glass barrels, thereby minimizing the amount of free silicone that can interact with drug product.").) Thus, a POSITA would have been motivated to use the baked-on silicone syringes in Boulange or [redacted] to improve the Macugen PFS and reduce the amount of free silicone oil in the drug product.

Another benefit of using baked-on siliconization over oily siliconization is that over time (*i.e.* during storage of the syringe), baked-on siliconization was known to have a lower increase in the break loose force. (JX-0306.0004.) Thus, a POSITA would be motivated to use the baked-on silicone technology of Boulange or [redacted] to achieve low break loose forces that would stay low over time.

The Staff also expects the evidence to show that adjusting the amount of silicone oil in a syringe was a routine optimization. For example, Dr. Sigg testified [redacted]. (Sigg Tr., 92:1-93:2, 186:12-187:5.)

Finally, Macugen PFS was already using [redacted]. A POSITA would reasonably expect to be successful in swapping out the [redacted] of the Macugen PFS for either the [redacted] or BD's Boulange syringe.

Novartis argues that "a POSA would not have been motivated to reduce the amount of silicone oil in the MACUGEN PFS unless the POSA had a high degree of confidence that doing so would not make the syringe mechanically unsuitable for intravitreal injections." (CPreBr. at 155.) But that confidence would have been provided by the results of Boulange and [redacted], both of which had break loose and glide forces that were suitable for intravitreal injection. For the same reason, Novartis is wrong that a "POSA would not have attempted to reduce it to below about 100 µg because, as discussed above, the prior art taught that such a dramatic reduction would likely compromise mechanical function." (*Id.*) Boulange and BD EZGTC both showed to persons of skill that a "dramatic reduction" could be achieved without compromising mechanical function. The fact that other prior art references might not have come to that discovery simply means Macugen PFS is not obvious in combination with those other, high-silicone oil references; but the

disclosure of those references does not somehow cancel out the disclose of Boulange and [redacted].

With respect to Boulange, Novartis argues that a POSITA would not have used Boulange because of the unknown effects of Parylene C. (CPreBr. at 156-57.) But as explained above, Boulange offered non-Parylene C options, and a POSITA would simply pick those options if they had some concern with using Parylene C. (*See supra* at 67.)

f. Secondary considerations

Novartis asserts that the secondary considerations of commercial success, licenses, long-felt unmet need, industry praise, skepticism, and failure of others weigh against a finding of obviousness. (CPreBr. at 159-177.) The Staff examines each consideration below.

(1) Commercial Success

The Staff does not dispute that Lucentis PFS practices certain claims of the '631 patent,[32] or that Lucentis PFS was commercially successful. But in the Staff's view, Novartis has not shown that the commercial success of Lucentis PFS was due to a claimed feature that was not already known in the art prior to the '631 patent. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed

[32] *See* CPreBr. at 226-231.

invention.") (emphasis in original); *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed.Cir.2011) ("If commercial success is due to an element in the prior art, no nexus exists."); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent"); *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) ("[T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art.")

In the Staff's view, the evidence will show that the success of Lucentis was driven by the efficacy of the drug substance, not the PFS format. For example, during his deposition Novartis's expert Dr. Calman explained that the switch from Macugen to Lucentis (where Macugen was available in a PFS and Lucentis was only available in a vial) was due to the efficacy of the drug, not the PFS format. Moreover, none of Novartis's cited evidence establishes that Lucentis PFS was commercially successful because of the features that were allegedly not found in the prior art, *i.e.* a terminal sterilization and 1-100 μg of silicone oil with break loose forces less than 11N.

Novartis also argues that the nexus between commercial success of Lucentis PFS and the claimed features is demonstrated by "terminal sterilization and low silicone oil levels, [that] were necessary to obtain FDA approval." (CPreBr. at 166.) But drugs are not necessarily commercially successful because they are approved by the FDA; FDA approval is merely a necessary (not sufficient) condition for

commercial success. Thus, the fact that certain features of a claimed invention may relate to product features required for FDA approval does not mean that the subsequent success of the product is related to the claimed features. Moreover, Macugen PFS was a terminally sterilized and siliconized syringe approved by the FDA. Thus, the FDA's approval could not have hinged on the claimed features of the '631 patent (which Novartis asserts were lacking in Macugen PFS).

Novartis also argues that both Lucentis and Eylea experienced increased demand when they switched from a vial to a PFS format. (CPreBr. at 167.) But that cannot show the non-obviousness of the claimed invention because a PFS presentation for a VEGF-antagonist was already known in the art, Macugen PFS. Novartis offers no additional evidence to show that it was the claimed features of the '631 patented PFS that drove the uptake of Lucentis PFS (as opposed to simply a preference for the known prior art PFS presentation and the effectiveness of the drug substance).

(2) Licensing

Novartis asserts that [redacted] licenses show the non-obviousness of the '631 patent, those with Genentech [redacted]. (CPreBr. at 168.) As an initial matter, it is unclear to the Staff that [redacted] licenses, one of which is [redacted] can constitute such substantial licensing activity as to show the non-obviousness of the patent. *See Metabolite Lab'ys, Inc. v. Lab'y Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004) (eight licenses found to support non-obviousness).

With respect to the Genentech patent, Novartis does not put forward evidence that the license was primarily driven by the '631 patent. The extensive terms of the agreement make clear it encompassed a [redacted] and [redacted] that goes [redacted]. (CX-0010C; CX-0013C.) The license also appears to cover a [redacted] the '631 patent, which additionally shows that the license does not support a finding of non-obviousness. (CX-0012C.0021.) To the extent that Novartis is correct that Genentech needed [redacted] to bring the Lucentis PFS to market, the evidence put forward by Novartis fails to show that it was because of the '631 patent, rather than technical know-how and support transferred from Novartis to Genentech. (CX0011C.0003 (noting that after payment by Genetech, "Novartis will deliver the [redacted] and [redacted] to Genentech"); CX-0012.0011-15, 0018-002 (setting out [redacted] Novartis will provide to Genentech).) Moreover, the license was a [redacted] as well. (CX-0010C.0038.) In the Staff's view the Genentech license provides little or no evidence of non-obviousness.

The [redacted] license is a [redacted] license for an [redacted] ot [redacted] to sell [redacted] (CX-1061C.) But of course, [redacted] does not need a license to the '631 patent to sell [redacted] Moreover Novartis cites to no evidence to show that the value of the [redacted] license was driven by the '631 patent specifically, as opposed to any [redacted], or as

opposed to the value of the [redacted]. Thus, the Staff does not expect the [redacted] license to show the non-obviousness of the '631 patent.

(3) Long-felt unmet need and industry praise

In the Staff's view, the evidence will show that to the extent there was a long felt need for a PFS for VEGF-antagonists, that need was met by Macugen PFS. Further, the evidence put forward by Novartis does not show that there was a long-felt but unmet need for the claimed features of the '631 patent, and that Lucentis PFS met that need. For example, CX-1286 states that Dr. John Thompson found (in 2019) that he did not observe any silicone oil in a small group of eyes that were injected with "prefilled, silicone-free ranibizumab syringes" and thus recommended using "silicone-free syringes." (CX-1286.0001.) Using a "silicone-free" syringe does not show the non-obviousness of the '631 patent.

Novartis also relies on JX-0499, an article reviewing the Lucentis PFS, asserted that it has "specific reference to the reduction of infection risk and of silicone oil levels." (CPreBr. at 172.) But the article touts the advantages of a PFS for intravitreal injection generally, not specifically the claimed PFS invention; as explained above, the Macugen PFS was already in the art. For example, the article mentions a possible reduction of injection risk with a PFS as compared to a vial, but it does not highlight any specific sterility features of Lucentis PFS. (JX-0499.0003.) Similarly, the article refers to a possible "theoretical" benefit of lower silicone oil compared to injections given with insulin syringes and explains that it was likely because Lucentis PFS used a "baked silicone" process. (*Id.* at 0004.) But syringes

with baked-on siliconization were known in the art, including for pre-filled syringes (such as those disclosed by [redacted] or Boulange). Moreover, nothing in the article suggests praise for the specific "low" silicone range claimed by the '631 patent; rather, the article appears to be praising the use of the well-known baked-on siliconization process.

(4) Skepticism of others

Novartis points to the skepticism from Vetter regarding whether a syringe with less than 100 µg of silicone oil could achieve "functional stopper forces" as evidence of non-obviousness. (CPreBr. at 173.) The Staff does not agree that shows non-obviousness. First, Vetter was already in possession of a syringe within the range claimed by the '631 patent (*i.e.* with [redacted] of silicone oil and break loose force less than 11N). The Staff does not believe the skepticism of a party about particular claim limitations, where that party had already conceived of a device that met the claim limitations in question, can show that the claims are non-obvious.

Second, while Vetter maybe have been skeptical, BD had already made public syringes with less than 100 µg of silicone oil and break loose force less than 11N, *i.e.* Boulange and [redacted]. The fact that one group of engineers at Vetter was skeptical of a possibility that was already in the art is not evidence that the '631 patent was not obvious.

(5) Failure of others

Novartis asserts that the [redacted] indicates the non-obviousness of the '631 patent. (CPreBr. at 173-177.) The Staff disagrees. First,

and as explained below, the Staff agrees that Regeneron reduced to practice a PFS meeting the asserted claim limitations (other than 24 and 25) by June 2010.[33] (*See* Section IV.D.3.) And as explained above with respect to the obviousness of claims 24 and 25, physicians were successfully using Macugen PFS to treat wAMD prior to the '631 patent. (*See supra* at 89.) Thus, there was not a failure of others.

Second, Novartis's arguments with respect to Genentech detail how Genentech [redacted] a PFS. (CPreBr. at 174 ("The evidence will show that Genentech [redacted]"). But Eyetech succeed in doing so with Macugen PFS. Thus, Genentech's [redacted] a PFS is simply evidence of Genentech's [redacted]. Success by Eyetech and Regeneron show that there was no "failure of others" sufficient to prove the non-obviousness of the '631 patent.

2. Inventorship Under 35 U.S.C. § 102(f)

In the Staff's view, there will be clear and convincing evidence that the '631 patent is invalid for improper inventorship. The Staff bases this conclusion on two related but independent grounds: (a) employees of Vetter [redacted]

[33] Novartis argues that Regeneron failed because it could not "demonstrate adequate stability and purity over time." (CPreBr. at 174.) As explained with respect to Regeneron's § 102(g) defense below, the Staff does not believe this argument is relevant because the claims do not require "adequate stability and purity over time."

[redacted] (b) Vetter employees contributed in a significant manner to the conception [redacted]

a. Vetter employees [redacted]

The evidence is expected to show that employees of Vetter [redacted]

The evidence will show that employees of Novartis (including some of the named inventors such as Dr. Sigg) visited Vetter's facilities in December of 2006; a January 8, 2007, memorandum authored by [redacted] of Novartis (and copying Dr. Sigg) followed up on the meeting and explained Novartis's understanding that Vetter could provide a "[redacted]"[34] (JX-0094C.0002.) Similarly, an August 2009 presentation written by [redacted] of Vetter describes that Vetter's siliconization process for a [redacted] resulted in "actual amounts of silicone oil per syringes of approx. [redacted]." (JX-0076C.0004.) The same presentation explains that those Vetter siliconized syringes had "break loose forces …. up to [redacted]." (JX-0076C.0004.) Moreover, a 2013 report on the Lucentis project written by Dr. Sigg noted that "[a]t start of the project, established best process at the selected contract development and manufacturing site, Vetter Pharma-Fertigung GmbH (Ravensburg and Langenargen, Germany), yielded an

[34] *I.e.* [redacted] per syringe.

average of [redacted] silicone oil in the syringe." (JX-0050C.0005.; JX-0416, Sigg Tr., at 175:3-18.)

In sum, the evidence is expected to show that employees of Vetter, not the '631 patent named inventors at Novartis, [redacted] In the Staff's view, that evidence alone shows that Vetter "(1) contribute[d] in some significant manner to the conception or reduction to practice of the invention, (2) ma[de] a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and (3) d[id] more than merely explain to the real inventors well-known concepts and/or the current state of the art." *See Pannu*, 155 F.3d at 1351.

First, Vetter contributed in a significant manner to the conception and reduction to practice of the invention by [redacted] Testimony from Dr. Sigg and [redacted] is expected to show that the Novartis inventors were (a) aware of Vetter's [redacted] of silicone oil process, and (b) wanted to go lower than that. (JX-0416, Sigg Tr., at 154:8-14, 155:3-20; JX-0415, [redacted] Tr., at 59:2-16, 62:4-13.) But it appears that Vetter unquestionably [redacted] that were ultimately claimed in the '631 patent. The Staff views that as contributing in a significant manner to the conception (and reduction to practice) of the invention.

Second, the same evidence shows that Vetter made a contribution to the claimed invention that was not insignificant in quality, when that contribution is measured against the dimension of the full invention. The full syringe invention as claimed by claim 1 of the '631 patent has approximately six elements:

(1) terminally sterilized;
(2) fill volume between 0.5 and 1 ml;
(3) between 1 and 100 µg of silicone oil;
(4) contains a VEGF-antagonist;
(5) VEGF-antagonist has no more than 2 particles >50 µm in diameter per ml; and
(6) stopper break loose force of less than 11N.

As explained above, Vetter made a significant contribution to [redacted] Prefilled syringes with 0.5 or 1 ml fill volumes were known in the art.[35] The (4) "VEGF-antagonist" provided in a pre-filled syringe was available in the prior art, and thus was not contributed by Vetter or Novartis.[36] The particulate matter limitations came from the known USP 789 standard.[37] And the (1) terminal sterilization process used by the inventors was already known in the art. (Sigg Tr., at 72:8-12; '631 patent, 9:49-52 ("As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a *known process*

[35] Macugen PFS and [redacted] were 1 ml prefilled syringes known in the art. (*See* Sections IV.D.1.a.(3)-(4).)

[36] For example, Macugen PFS was a VEGF-antagonist drug provided in a prefilled syringe and on sale by 2004. (*See* Sections IV.D.1.a.(4) & IV.D.1.e.)

[37] [redacted]. (JX-0004C.0211.)

such as an ethylene oxide (EtO) or a hydrogen peroxide (H_2O_2) sterilisation process").) Thus, measured against the "full invention," the Staff believes the evidence will show that Vetter's contribution is not insignificant in quality.

Third, the Staff does not believe the evidence will show that Vetter was merely explaining the prior art or the state of the art.[38] In particular, the '631 patent asserts that "[b]reak loose and slide forces for pre-filled syringes known in the art are typically in the region of *less than 20N*, but where the pre-filled syringes contain about 100 µg-about 800 µg silicone oil." ('631 patent, 5:35-38 (emphasis added).) Vetter, however, [redacted] which was below the prior art value (and was ultimately the claimed value). Thus, the evidence is expected to show that Vetter was not merely explaining to Novartis the prior art.

Thus, the Staff expects the evidence to show that one or more employees at Vetter should have been named as inventors of the '631 patent based on their significant contribution to at least claim 1.

[38] As explained above, the Staff believes the evidence will show that all the elements of the '631 patent were known in the prior art. But it does not appear from the evidence that Vetter was explaining said prior art to Novartis (or was even aware of it).

b. Vetter employees contributed to the [redacted]

In addition to contributing to the [redacted], the Staff expects the evidence to show that Vetter made a significant contribution to the [redacted].

As noted above, the evidence is expected to show that Novartis employees were aware of Vetter's [redacted] of silicone oil syringe but wanted something lower than that. Additionally, the evidence will show that the minimum boundary that the Novartis inventors had conceived prior to working with Vetter was [redacted], though the Novartis inventors were aware that [redacted]. (Sigg Tr., at 155:22-156:11, 222:11-223:11.) The Staff is not aware of any evidence to show that the Novartis inventors had [redacted].

Thus, the evidence will show that in approximately 2009, Novartis had already formulated a general idea for a syringe with less silicone oil than Vetter's standard [redacted] of silicone oil syringe, but more than zero silicone oil. (RX-1061.0002; JX-0415, Rotelle Tr., at 77:13-79:13.) The evidence is further expected to show that in 2009, Novartis communicated this general plan to Vetter (*see id.*), and asked Vetter to determine the minimum silicone amounts that would still result in "acceptable" break loose forces (JX-0091C.0003). And with respect to the break loose force, the evidence is expected to show that Novartis provided an upper

limit based on the break loose force for existing non-prefilled syringes.[39] ([redacted] Tr., 85:19-86:18.)

The evidence is expected to the show that starting in approximately the summer of 2009 and going until the spring of 2011, Vetter employees ran a series of experiments in which they tested the existing [redacted] of silicone oil syringe and then experimented with different [redacted] to develop syringes with silicone amounts ranging from down to about [redacted] and up to about [redacted]g. (JX-0073.0005-0006; JX-0076; JX-0075.0011, 0014 (identifying variants tested and showing break loose force results of less than 11N for all but one sample); JX-0387C.0002-4 (Nov. 2009 Vetter report showing several [redacted] with total silicone amounts including approximately [redacted] and less than [redacted]); JX-0060 (email from Vetter to Novartis explaining that results of Nov. 2009 test report [JX-0387C] showed "[b]reak loose and gliding forces in general are acceptable for all variants tested"); JX-0086.0008-9 (identification of additional dilutions tested).)

The evidence is expected to show that in the fall of 2010, a report by [redacted] of Vetter indicated that Vetter had developed a syringe with between [redacted] and [redacted] of silicone, with an average of [redacted], and break loose forces and glide forces under [redacted]. (JX-0400.) Moreover, by April 11, 2011, the evidence will show that Vetter had conceived of and reduced to practice a syringe with "approx [redacted] [of silicone oil] … applied over the entire syringe length." (RX-1079.0003.) This

[39] As explained above, Vetter was already in possession of a syringe barrel with break loose forces less than 11N.

syringe, which used a [redacted], resulted in break loose and glide forces less than [redacted]. (*Id.* at 0007.) The report summarizes the result of the siliconization study:

> [T]hese silicone oil values are much lower than a standard baked on siliconization which are normally known for delivering low silicone oil values.
>
> Consequently this systematic study showed that the chosen target parameters with their specified ranges lead to a robust siliconization process which delivers a low amount of silicone oil per syringe. The low variability in silicone oil content is not critical in terms of product stability and syringe functionality therefore the process parameters are acceptable and fulfil the requirements for the product.

(*Id.* at 0016.)

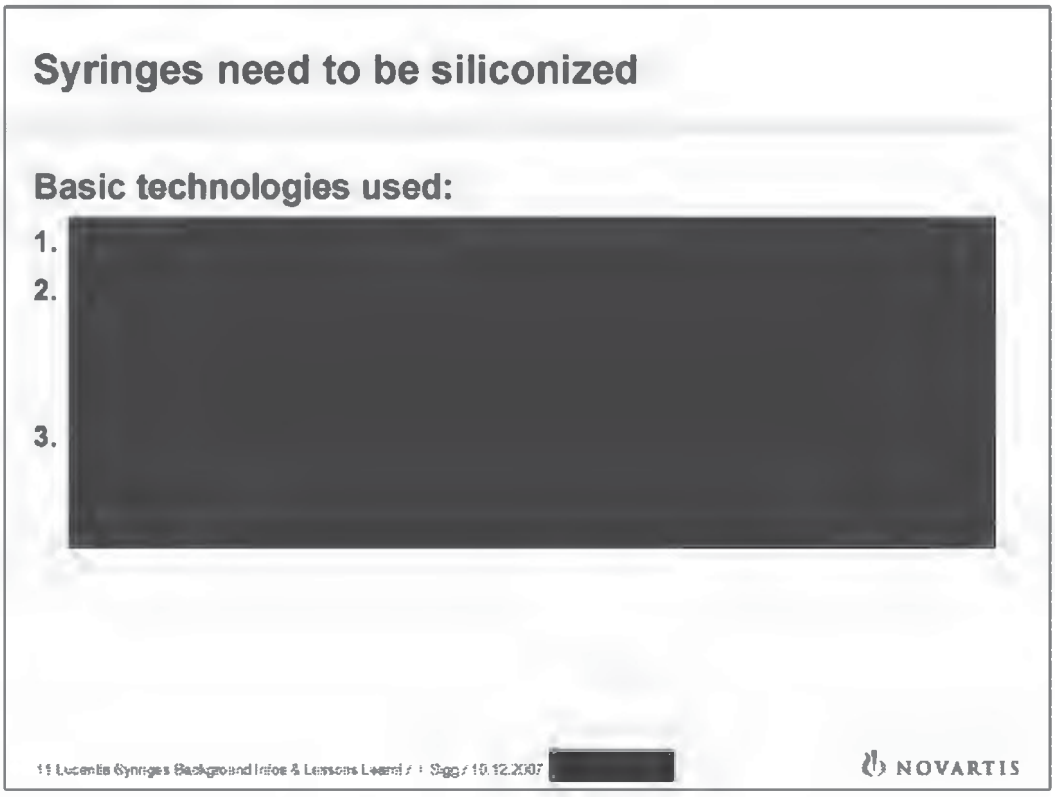
Set against that record of Vetter's contribution, the Staff is not aware of any evidence that the named Novartis inventors [redacted]

c. Novartis's position

Novartis first argues that Vetter was acting as a contract manufacturer (or "CMO") on the project and that any experiments they performed were at the direction of Dr. Sigg. (CPreBr. at 68.) In the Staff's view, while the economic relationship and management of the experiments may be relevant to the analysis, in and of themselves those facts do not answer the relevant question of who conceived of the silicone oil limitations.

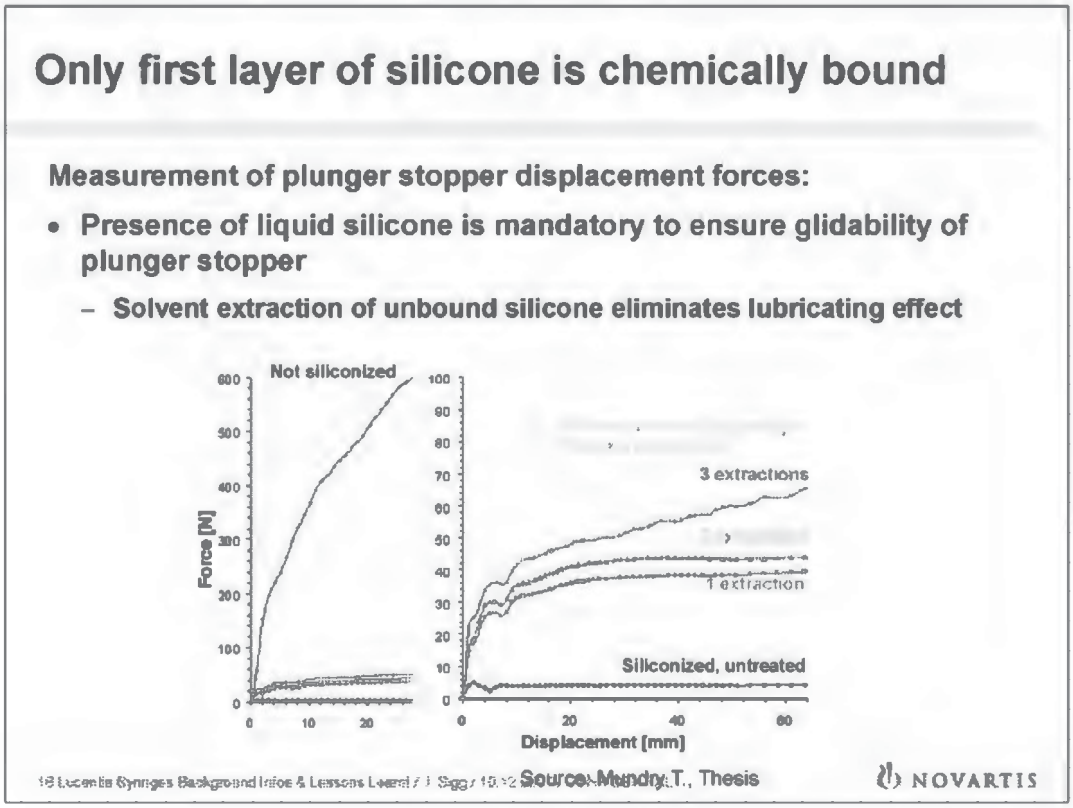
Novartis also argues that Dr. Sigg conceived of the upper limit of 100 µg of silicone oil by [redacted] based on a presentation he delivered titled "Lucentis

Pre-filled Syringes: Background Infos & Lessons Learnt from other Projects." (CX-1032C.) The Staff disagrees. First, the slides cited by Novartis do not on their face show that Dr. Sigg "believed that baked silicone could achieve silicone amounts less than [redacted] / barrel." (CPreBr. at 70.) The first slide, at CX-1032C.0011, simply explains that syringes need to be siliconized but does not identify any particular amount:



(CX-1032C.0011)

The next slide at CX-1032C.0016 does not identify any silicone amounts at all, and in fact appears to show charts pasted from the "Mundry T. Thesis."



(CX-1032C.0016)

Finally, the slide at CX-1032C.0018 identifies what Dr. Sigg believed were "Typical" values for oily and baked-on siliconization of 1 mL syringes. The presentation is dated December 10, 2007 (CX-1032C.0001), which is a year after the evidence shows Vetter informed Novartis that Vetter was in possession of a siliconized syringe with [redacted]. Thus, Dr. Sigg's reference to a "typical" syringe was referring to syringes known in the art (not something he conceived) and was likely a reference to the [redacted]. Additionally, the charts on the slide lack units of force, so it is not possible to know what break loose force is reflected on the charts.

(CX-1032C.0016)

The slides at CX-1032C therefore do not show that "Dr. Sigg had already conceived of the upper limit of 100 µg of silicone." (CPreBr. at 69.) As explained above, Dr. Sigg learned about the [redacted] of silicone syringe from Vetter.

The second problem with Novartis's contention is that it is contradicted by both documents from earlier than [redacted] and Dr. Sigg's deposition testimony. As noted above, a memo from January 2007 (a year before CX-1032C) indicated Novartis's awareness that Vetter had a [redacted] siliconized syringe. (JX-0094C.0002.) And that awareness is corroborated by Dr. Sigg's testimony that Novartis was aware in [redacted] or [redacted] that Vetter had a [redacted] of silicone oil syringe

with break loose force forces less than 11N. (Sigg. Tr. at 174:3-175:18.)[40] Thus, the record evidence is expected to contradict Novartis's contention that Dr. Sigg conceived of the [redacted]

Next, Novartis asserts that Dr. Sigg conceived of the claimed lower boundary based on his expected testimony that "as low as possible" meant "less than 100 µg but greater than zero." (CPreBr. at 70.) But the claims are not directed to "less than 100 but greater than zero." As a matter of simple logic, the lower limit encompassed by that range includes every integer from 99 down to 1. The silicone oil range claim elements have particular lower boundaries though, *i.e.* 1 µg and 3 µg, and [redacted].

Novartis also asserts that Vetter' skepticism about going lower than 100 µg shows that Vetter employees could not be co-inventors. (CPreBr. at 70-71.) But the evidence shows that when Vetter did perform the experiments, they were able to [redacted]). (JX-0387C.) At best then, this argument indicates that it required contributions from Vetter employees and Dr. Sigg to jointly conceive of the claimed 1-100 µg of silicone oil.

[40] In the cited testimony, Dr. Sigg is discussing Table 6 in Ex. 11 to Dr. Sigg's deposition, which has been marked as trial exhibit JX-0073C.

Novartis further asserts that the evidence will not show that [redacted] personally conceived of the limitations, and thus, cannot prove joint inventorship. (CPrebBr. At 71-72.) In the Staff's view, this misconstrues the issue. Under 35 U.S.C. § 102(f), a patent is invalid if the named inventors "did not … invent the subject matter sought to be patented." There is no carve out in the statute that allows patents to remain valid where the inventor did not invent the subject matter sought to be patented but the individual identities of the true inventors is not clear. *Cellular Commc'ns Equip. LLC v. HTC Corp.*, No. 6:16-CV-475-KNM, 2018 WL 4261195, at *3 (E.D. Tex. July 5, 2018) (denying plaintiff request for summary judgment on § 102(f) defense where defendant did not identify any putative missing inventor, finding that no case law had been identified that required such a showing and the defendant had put forward evidence that "calls into question whether [the named inventor] was the sole inventor of the subject matter of the claimed invention"). In other words, the '631 patent is invalid because it fails to include the proper inventors, including one or more persons at Vetter who jointly conceived of the claimed invention. And that conclusion follows from the clear and convincing evidence that Dr. Sigg and the other Novartis inventors [redacted]. Thus, while the evidence shows that *someone* at Vetter was a joint inventor, identifying the correct individual Vetter inventors will

only be necessary if a party asks the PTO or a district court to correct the inventorship of the '631 patent.[41]

Novartis also contends that the "significant inventive aspect of the silicone oil limitations was not the upper limit of 100 µg, but the discovery that levels significantly below that amount could achieve injection forces comparable to those seen in syringes siliconized with 100 µg or more of silicone oil while still allowing for effective terminal sterilization of the syringe."[42] (CPreBr. at 72.) That argument, however, ignores the fact that the *claimed* invention includes a 100 µg of silicone oil syringe with break loose force of 11N or less, and that such a syringe [redacted]. In other words, Novartis cannot claim 1-100 µg of silicone oil but argue that only 1-99 µg of silicone oil was the "inventive aspect." If 1-99 µg of silicone oil is what Dr. Sigg invented independent of Vetter, then that is what Novartis should have claimed.

And moreover, as explained above, Dr. Sigg may have had a "general plan" for going below 100 µg of silicone oil, [redacted]. *See Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223,

[41] As explained above, and detailed in Regeneron's Pre-Hearing Brief, the evidence shows that one or both of [redacted] appear to be the Vetter employees responsible for conception of the silicone oil range limitations.

[42] Novartis also appears to be implying that the claimed invention includes novel aspects related to terminal sterilization. In the Staff's view, however, any novel syringe features related to terminal sterilization may have been disclosed but were not claimed in the '631 patent. Thus, the "while still allowing for effective terminal sterilization of the syringe" is not an "aspect" of the claimed invention.

1228 (Fed. Cir. 1994) ("An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, *not just a general goal or research plan he hopes to pursue*") (emphasis added).

Finally, Novartis takes issue with Regeneron's reliance on the [redacted] dispute between Vetter and Novartis that was ultimately settled [redacted] (CPreBr. at 72-73.) In [redacted]

In particular, Federal Circuit case law requires a joint inventor to "contribute in some significant manner to the conception of the invention." *Fina Oil*, 123 F.3d at 1473 (emphasis added). [redacted] But the Staff believes the documents from [redacted], during the actual period of the Vetter and Novartis collaboration, are the more relevant evidence.

d. If inventorship is improper, then the '631 patent is unenforceable at the ITC

Novartis no longer appears to argue that the '631 patent cannot be invalid under 35 U.S.C. § 102(f) because inventorship can be fixed under 35 U.S.C. § 256. To the extent that issue is raised, however, the Staff agrees with Regeneron that the Commission does not have the authority to amend a patent under 35 U.S.C. § 256. Section 256 permits the Director of the PTO or a court to correct an issued patent. *See* 35 U.S.C. § 256; *Egenera, Inc. v. Cisco Sys., Inc.*, 972 F.3d 1367, 1376 (Fed. Cir. 2020). The ITC is neither of those things, and thus, lacks any statutory authority to correct inventorship. *See Certain Elec. Imaging Devices*, Inv. No. 337-TA-850, Comm'n Op., 2018 WL 11201935, at *48 (Nov. 1, 2018) ("The Commission does not have the authority to correct inventorship."). Moreover, because the "Commission has no power to correct inventorship, the [asserted] patent is unenforceable unless and until either the PTO or a court makes the 'correction.'" *EPROM, EEPROM, Flash Memory, and Flash Microcontroller Semiconductor Devices*, Inv. No. 337-TA-395, USITC Pub. 3392, Comm'n Op., at 9-10 (Jul. 9, 1998).

Thus, if the ALJ finds that that '631 patent is invalid under 35 U.S.C. § 102(f) (pre-AIA), then there must be a finding of no violation because the patent is unenforceable until the PTO or a court of general jurisdiction fixes the inventorship issue. *See* 19 U.S.C. § 1337(a)(1)(B) (infringement of a "*valid and enforceable* United States patent" constitutes a violation of Section 337 (emphasis added)).

3. Prior Invention By Another Under 35 U.S.C. § 102(g)

In the Staff's view, there will be clear and convincing evidence that Regeneron reduced to practice a PFS that met the limitations of claims 1, 3-6, 11-13, 16, 17, and 21 and 23 by June of 2010, but not claims 22, 24 or 25. It is the Staff's view, however, that there will be no clear and convincing evidence that Regeneron did not abandon, suppress, or conceal that invention prior to Novartis's conception.

a. Reduction to practice of claims 1, 3-6, 11-13, 16, 17, and 20-23

In the Staff's view, the evidence will show that Regeneron reduced to practice a PFS meeting all the limitations of claims 1, 3-6, 11-13, 16, 17, 21 and 23 by June of 2010.[43] There is not expected to be clear and convincing evidence that claims 22, 24, and 25 were reduced to practice.

As an initial matter, the Staff notes that it disagrees with Novartis's apparent argument that no one at Vetter or Regeneron "appreciated" that they had achieved the claimed invention. (CPreBr. at 85.) As will be shown below, the two companies' respective documents show that each claim limitation was met. To the extent the exact silicone amount was not expressed as a mass in micrograms, the

[43] Because Regeneron reduced to practice the invention before the '631 patent's conception date, the Staff does not believe the issue of conception is relevant. *See Perfect Surgical Techniques, Inc. v. Olympus Am., Inc.*, 841 F.3d 1004, 1015 (Fed. Cir. 2016) ("To establish priority of an invention, a party must show either an earlier reduction to practice or an earlier conception followed by a diligent reduction to practice").

Federal Circuit has explained that "[t]he reduction to practice test does not require *in haec verba* appreciation of each of the" claim limitations. *See Mycogen Plant Sci. v. Monsanto Co.*, 243 F.3d 1316, 1336 (Fed. Cir. 2001). Rather, it is sufficient to provide evidence that a product or process met all the limitations of the claims and that the resulting product was "appreciated to work for its intended purpose." *Id.* at 1337 (explaining that prior inventors "actions were clearly performed deliberately, with no suggestion of accidental invention"). There is no evidence that Vetter or Regeneron accidentally terminally sterilized an EYLEA PFS, or accidentally applied between 1 and 100 µg of silicone oil, or accidentally tested the break loose force.

To the contrary, the evidence identified below shows that Regeneron appreciated that the terminally sterilized EYLEA PFS would work for its intended purpose. As explained below, the evidence will show that Regeneron reduced the claimed PFS to practice by June of 2010 using a siliconized syringe provided by Vetter.

(1) Claim 1

1[preamble] A pre-filled, terminally sterilized syringe for intravitreal injection, the syringe comprising a glass body forming a barrel, a stopper and a plunger and containing an ophthalmic solution which comprises a VEGF-antagonist, wherein:

The Staff expects the evidence to show that in March and April of 2010, Regeneron manufactured several lots of EYLEA PFS, identified by the lot numbers C08011M640N11 (JX-0292C), C08012M640N11 (RX-1122C), and C08014M640N11 (RX-1123C.) The "Quality Assurance Batch Status Form" for each lot indicates that

each lot comprised approximately 25,000 1 mL syringes, which are identified as containing "VEGF Trap ITV Drug Product 40 mg/mL."[44] (JX-0292C; RX-1122C; RX-1123C.)

[redacted] and describes that it is the [redacted][45] (JX-0285C.0001.) That document shows that the EYLEA PFS had a glass barrel with a nominal fill volume of about 1ml and stopper that would be connected to a plunger. (*Id.* 0013.) According to the sBLA, the plunger is attached prior to blister packaging. (RX-1125C.)

The evidence will show that the batches of EYLEA PFS with lot numbers C08011M640N11, C08012M640N11, and C08014M640N11 (RX-1120C.0005) were terminally sterilized on June 22, 2010, June 23, 2010, and June 21, 2010, respectively, at Steris Corporation in Syracuse, NY using a vaporized hydrogen peroxide process. (JX-0292C.0004; RX-1122C.0005; RX-1123C.0004.) Regeneron reported to the FDA in the sBLA that each of these lots was sterilized using hydrogen peroxide. (JX-0347C.0019.)

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[44] "VEGF Trap" is another name for aflibercept, the active ingredient in EYLEA. ('631 patent, 6:36-40.)

[45] Regeneron's sBLA for EYLEA PFS identifies "Document Number [redacted]" as describing the overall process for manufacturing EYLEA PFS. (RX-1120C.0004.)

Novartis contests that this limitation was not reduced to practice by June 2010 because "terminal sterilization as recited in the '631 Patent requires ensuring through stability testing that the sterilizing agent has not affected the drug product, and someone could only 'get definitive proof' of this after stability testing," [redacted] (CPreBr. at 85.) As an initial matter, Novartis's only evidence in support of that characterization of the '631 patent is the testimony of Regeneron's expert Mr. Agallaco. (CX-1222C.) To the extent that is an accurate characterization of Mr. Agallaco's testimony, the Staff disagrees that it is an accurate characterization of the claims of the '631 patent. Nothing in the claims or specification requires "ensuring through stability testing that the sterilizing agent has not affected the drug product," nor has Novartis ever proposed that the claimed "terminally sterilized" PFS requires "stability testing."[46]

Additionally, Novartis's argument confuses the requirements the FDA imposes on a new drug product with the legal requirements to show a reduction to practice. (CPreBr. at 86 ("[redacted]").) As the Federal Circuit has pointed out "[o]ur cases distinguish between the standard required to show that a particular invention would work for its intended purpose and the standard that governs FDA approval of new drugs, including the various stages of clinical trials."

[46] The phrase "stability test" does not appear in the specification or claims of the '631 patent.

Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc., 855 F.3d 1356, 1372 (Fed. Cir. 2017). The court went on to contrast the testing required for a reduction to practice as compared to FDA required testing:

> Generally there must be some demonstration of the workability or utility of the claimed invention. This must show that the invention works for its intended purpose beyond a probability of failure but not beyond a possibility of failure. Later refinements do not preclude reduction to practice, and it is improper to conclude that an invention is not reduced to practice merely because further testing is being conducted.
>
> Approval of a new drug by FDA, however, is a more demanding standard than that involved in the patents-in-suit. … For FDA approval, however, an applicant must submit, inter alia, "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use" and "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed." 21 U.S.C. § 355(d). This requires "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." *Id.* This is understood to be a rigorous standard.

Helsinn Healthcare, 855 F.3d at 1372.

Here, the evidence is expected to show that the lots manufactured in June 2010 were "terminally sterilized" to the extent required to show that they worked for their intended purpose, [redacted]. For example, the lot numbers identified above were used to support the approval of EYLEA PFS in Europe and Australia. (RPreBr. at 105.) Moreover, evidence will show that the same terminal sterilization process used on the batches above was used to

terminally sterilize EYLEA PFS units used in clinical studies. (JX-0288C.0052-53; RX-0666C.0001-5.)

1(a) the syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml,

The Staff expects the evidence to show that the lots identified above had a nominal fill volume of 1 mL. (JX-0285C.0013.)

1(b) the syringe barrel comprises from about 1 µg to 100 µg silicone oil,

The Staff expects the evidence to show that the lots identified above had between about 1 and 100 µg of silicone oil in them. [redacted]

[47] Another copy has been marked as RX-1126C. That copy does not have any redacted names, but it appears to be missing pages.

[redacted]

Novartis does not dispute the accuracy of Dr. Sawyer's calculations, but rather asserts that various other documents show that [redacted]

[redacted]

48 [redacted]

[redacted]

1(c) the VEGF antagonist solution comprises no more than 2 particles >50 µm in diameter per ml and wherein the syringe has a stopper break loose force of less than about 11N.

The Staff expects the evidence to show that the syringes in Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 each had no more than 2 particles >50 µm. [redacted]

(2) Claim 3

As explained above, Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 had between 3 and 100 µg of silicone oil.

(3) Claim 4

As explained above, Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 used a DC 365 emulsion.

(4) Claim 5

As explained above the "Certificate of Analysis" for each Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 will show that the syringes had no more than 5 particles per ml ≥ 25 µm and no more than 50 particles per mL ≥ 10 µm. (JX-0292C.0005; RX-1122C.0004; RX-1123C.0004.)

(5) Claim 6

The same evidence put forward for claim 1(c) and claim 6 shows that the Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 met the USP 789 standard. (JX-0292C.0005; RX-1122C.0004; RX-1123C.0004; JX-0048; RX-1053; JX-0048.)

(6) Claims 11-13

The Staff expects the evidence to show that in the "Quality Assurance Batch Status Form" for each lot indicates that each lot comprised approximately 25,000 1 mL syringes, which are identified as containing "VEGF Trap ITV Drug Product 40 mg/mL." (JX-0292C.0001; RX-1122C.0001; RX-1123C.0001.) Moreover, the '631 patent identifies "aflibercept (Eylea®), which has recently been approved for human use and is also known as VEGF-trap" as a "non-antibody VEGF antagonist." ('631 patent, 6:36-40.)

(7) Claim 16

Similarly, the "Certificate Of Analysis" for each of Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 shows that those syringes had an approximately [redacted] "Sustaining forces." (JX-0292C.0004; RX-1122C.0005; RX-1123C.0004).

(8) Claim 17

[redacted]

(9) Claim 21

The expects the evidence to show that each of Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 achieved a sterility assurance level of 10^{-6}.

[redacted]

(10) Claim 22

As explained above, the Staff agrees with Novartis that there is some ambiguity in the Vetter (and Regeneron) documents about the precise amount of silicone oil on the syringes. While the Staff agrees that the amount of silicone was

between 1 and 100 (and between 3 and 100), the Staff does not believe there will be clear and convincing evidence that the amount was between 1 and 50. [redacted].

(11) Claim 23

As explained above, the Batch Nos. C08011M640N11, C08012M640N11, and C08014M640N1 used a DC 365 silicone emulsion. (JX-0285C.0011.) The '631 patent explains that DC 365 had a viscosity of about 350 cP. ('631 patent, 5:9-13.)

(12) Claims 24 & 25

In the Staff's view, there will not be clear and convincing evidence that Regeneron reduced claims 24 and 25 to practice prior to the '631 patent's priority date. Regeneron argues that it would have "been obvious" to use EYLEA PFS in a way that meets claims 24 and 25. (RPreBr. at 100, 102.) Similarly, Dr. Kiss is expected to testify that it would have been "obvious" for a physician to practice claims 24 and 25 using the EYLEA PFS reduced to practice in June of 2010. But the fact that it may have been "obvious" to perform the method claim is not clear and convincing evidence that Regeneron actually "performed a process that met all

the claim limitation[s]," which is what the statute requires. *See Fox Grp.* 700 F.3d at 1306.

b. Regeneron abandoned, suppressed, or concealed the invention

In the Staff's view, Regeneron will not be able to show clear and convincing evidence that it did not abandon, suppress, or conceal the invention in the nine year period between the reduction to practice of the EYLEA PFS in June 2010 and the commercialization of the same in December 2019.

First, it is not disputed that while Regeneron's original Biologics License Application ("BLA") for EYLEA included the vial and PFS presentation, the PFS presentation was withdrawn in August of 2011 [redacted] (JX-0286C; JX-0406C, Van Plew Tr., at 103:3-7; 140:9-13, 141:12-142:21.)

[redacted]

Third, the evidence will show that much of the delay in commercializing the EYLEA PFS was due to [redacted]

[redacted]

The Staff believes that the evidence described above does not show by clear and convincing evidence that Regeneron did not abandon, suppress, or conceal the EYLEA PFS. [redacted]

Taking into consideration the policy of rewarding the later inventor that promptly files for a patent over the earlier inventor who does not disclose,[49] and considering the evidence identified above, the Staff does not believe it would be equitable to invalidate Novartis's '631 patent filed in October of 2012 based on a reduction to practice by Regeneron that was not made public until December of 2019. *See Checkpoint Sys.*, 54 F.3d at 761 ("[A] determination of abandonment, suppression, or concealment has consistently been based on equitable principles and public policy as applied to the facts of each case").

c. Earlier conception by Novartis

Novartis attempts to swear behind Regeneron's § 102(g) defense by showing that Dr. Sigg conceived of the invention before June 2009. As an initial matter, the Staff agrees that this contention is improper. Novartis's contentions did not disclose that Dr. Sigg conceived of the claimed invention by himself by June 2009 conception date. The contentions did assert a September 2006 conception date, but that contention was nothing more than a string cite, and it did not explain that Dr. Sigg was allegedly the sole inventor. Instead, the contentions explained and provided support for an October 2011 conception date. Thus, in the Staff's view, Novartis should not be permitted to assert a conception date earlier than October 2011.

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[49] *W.L. Gore & Assocs.,* 721 F.2d at 1550 ("Early public disclosure is a linchpin of the patent system. As between a prior inventor [who does not disclose] and a later inventor who promptly files a patent application ..., the law favors the latter.").

Substantively, the Staff does not agree that Dr. Sigg alone conceived of the invention by June 2009, because the evidence will show that, at best, Dr. Sigg jointly conceived of the silicone oil limitations with employees of Vetter. (*See* Section IV.D.2.) The contention is also contradicted by Dr. Sigg's own testimony that all the named inventors contributed to claim 1. (Sigg Tr., 59:21-60:9.) Ms. Picci testified that she did not even join the project until the beginning of 2011. (JX-0417C, Picci Tr., at 20:5-7.) Thus, if Dr. Sigg is correct, [redacted].

Finally, because the Staff believes that Regeneron cannot show by clear and convincing evidence that it did not abandon, suppress, or conceal the EYLEA PFS that was reduced to practice in June 2010, it is unnecessary to establish the date of conception by Novartis.

4. Enablement and Written Description Under 35 U.S.C. § 112, ¶ 1

a. Enablement of the "VEGF-antagonist" limitation

Regeneron argues that the claim term "VEGF-antagonist" is a functional claim limitation that covers a "broad genus of unspecified substances that are defined solely by their function," and because the '631 patent does not enable a POSITA to make and use every possible VEGF-antagonist in that genus, the claims are not enabled. (RPreBr. at 205.) For the reasons below, the Staff disagrees.

As an initial matter, the Staff does not dispute the expected testimony of Regeneron's expert Dr. D'Amore regarding the broad scope of the term "VEGF-antagonist." (RPreBr. at 212-214.) Nor does the Staff dispute Dr. D'Amore's

expected testimony that "undue experimentation" would be required to discover every "VEGF-antagonist" that existed. (*Id.* at 214-217.)

The Staff disagrees with Regeneron, however, that Dr. D'Amore's testimony has any relevance to the enablement of the '631 patent's claims. It is undisputed that the patented invention is a syringe. Thus, the relevant question is not whether it would require undue experimentation to create new VEGF-antagonists (as Regeneron contends), but rather, whether it require undue experimentation to build the patented syringe with any given VEGF-antagonist. Regeneron presents no evidence to suggest that the particular properties of any given VEGF-antagonist would require undue experimentation to, for example, siliconize the syringe with 1-100 μg of silicone oil or terminally sterilize the syringe. In other words, whatever the breadth "VEGF-antagonist," the only important properties are those that impact putting the medicine into a syringe.

In the Staff's view the evidence will show that only routine experimentation would be required to adjust the claimed PFS for any given VEGF-antagonist, because such knowledge was in the prior art already. *See Trustees of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018) ("[T]he artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.") (internal quotation and citation omitted). For example, the evidence will show that it would be within the skill of a POSITA to adjust the slide force of the claimed PFS to

account for different viscosities of the solutions therein. (RPreBR. at 135.) Beyond adjusting the syringe to account for different viscosities of solutions a new VEGF-antagonist might come in, the Staff is not aware of any other major technical challenges a POSTIA would face in adjusting the claimed syringe to a different drug. More importantly, Regeneron does not offer clear and convincing evidence of any such issues.

The Staff believes the following hypothetical illustrates the flaw in Regeneron's argument. If the "VEGF-antagonist" elements were removed from claim 1, the scope of claim 1 would then broaden such that it covered a terminally sterilized PFS with the claimed mechanical properties but could be filled with any substance, *e.g.* some other drug for intravitreal injection, or water, or any other substance that could conceivably be placed in a PFS. It would be illogical to argue that such an open-ended claim (with respect to the substance in the syringe) was not enabled because a POSITA would be unable to synthesize every single chemical, liquid, gas, etc., that could theoretically be placed into the syringe. Instead, the proper inquiry would be whether the specification enabled the syringe itself to be made and used, and whether the prior art (*i.e.* what was already known) would enable the POSITA to adjust the syringe for whatever substance they would (or could) put into it.

The fact that the '631 patent is more narrowly drawn to a PFS with a VEGF-antagonist (compared to the hypothetical claim above) does not mean it is not enabled. Rather it simply means the specification need only teach how to make and

use a claimed syringe with a VEGF-antagonist in it (rather than a syringe with anything in it). As noted above, the specification concedes that several VEGF-antagonists were already known in the art. Regeneron presents no evidence that it would require undue experimentation to adjust the claimed syringe for any given VEGF-antagonist, whether the drug was new or already known.

Thus, the Staff does not believe there will be clear and convincing evidence that the '631 patent claims are not enabled.

b. Written description of the "VEGF-antagonist" limitation

Regeneron also asserts that the "VEGF-antagonist" limitation lacks sufficient written description for largely similar reasons as Regeneron's enablement argument, *i.e.* the specification does not describe "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus." (RPreBr. at 218 (*citing Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc)).) For the same reasons expressed above, the Staff disagrees.

Regeneron's argument assumes that the written description that is required here is a written description of all VEGF-antagonists. But what is claimed is a syringe that contains a VEGF-antagonist. Thus, the relevant inquiry is whether the written description conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventors were in possession of the claimed syringe which can contain a VEGF-antagonist, and demonstrates that by disclosure

in the specification. *See Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1376–77 (Fed. Cir. 2019).

Regeneron does not present any evidence to show that a POSITA would have believed, based on the specification, that the inventors were not in possession of a syringe that contained a VEGF-antagonist. To the contrary, the specification provides sufficient information for a POSITA to recognize that the inventors were in possession of a syringe with the claimed properties, and which was physically capable of containing any particular VEGF-antagonist. (*See e.g.* '631 patent, 10:56-12:20.)

c. Enablement of the silicone oil range

Regeneron argues that the claims are invalid because the "specification does not teach or disclose any process for applying silicone oil to a syringe barrel—let alone a process for applying amounts as low as 'about 1 µg' or 'about 3 µg' of silicone oil on the barrel of a 0.5 ml to 1 ml glass syringe, while maintaining break loose and slide forces within the claimed ranges." (RPreBr. at 222.)

The Staff expects testimony from Dr. Sigg to show that it was well known prior to the '631 patent that low amounts of silicone oil could be achieved by simply by diluting a baked-on silicone oil emulsion with additional water. (Sigg Tr. at 92:1-93:2, 186:12-187:5, 220:13-21.) More, the evidence is expected to show that undue experimentation would not be required to achieve the claimed break loose and slide forces with amounts as low as "about 1 µg" or "about 3 µg." Vetter engineers required only two months to conceive of (and reduce to practice) a syringe with less

than [redacted] of silicone oil and break loose and slide forces less than 11 N. (CX-1017C.0002-4; CX-1024.0005, 11, 14-20; CX-1048C.0003-4; CX-0203C.0001-2.)

Regeneron's response to this evidence is to suggest that even after extensive research, Vetter ultimately concluded "[redacted] of silicone oil was the minimum amount required for a commercial process." (RPreBr. at 224.) But of course, the standard for enablement is not that a POSITA must be able to make and use a "commercially" viable version of the invention. *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 684 (Fed. Cir. 2015) ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment, so the time it took to make a commercial-grade embodiment is not, itself, determinative of non-enablement.") (internal citations and quotation marks omitted); *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003) ("Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace"). The evidence above shows that Vetter was able to make and use a prototype of a syringe with less than [redacted] of silicone oil and break loose force less than 11N, in only two months.

Thus, the Staff expects the evidence to show that undue experimentation is not necessary to make and use the lower end of the silicone oil range claims. Therefore, there is not expected to be clear and convincing evidence that the claims are not enabled.

5. Indefiniteness Under 35 U.S.C. § 112, ¶ 2

Regeneron's Pre-Hearing Brief asserts that it "incorporates in full all of the claim construction briefing, arguments, testimony, and evidence in this Investigation, and reserves all rights to argue as such at the hearing, to the Commission, or on appeal." (RPreBr. at 225.) In the Staff's view, Regeneron's failure to "set forth in detail" an indefiniteness defense in its Pre-Hearing Brief means that Regeneron has waived the issue. (Ground Rule 11.2.) To the extent Regeneron is permitted to assert an indefiniteness defense based on incorporating its *Markman* brief, the Staff incorporates in full the Staff's response to that defense in the Staff's *Markman* brief. (EDIS Doc ID 725440.)

E. Other Defenses

The Staff notes that Regeneron's Response pleads the defense of "Unclean Hands." (Response at 20-21.) As Regeneron has not addressed the "Unclean Hands" defense in its Pre-Hearing Brief, that defense has been waived. (Ground Rule 11.2.)

V. DOMESTIC INDUSTRY – ECONOMIC PRONG

A. Overview of Novartis's Domestic Activities

Novartis's activities in the U.S. are related to Novartis's VEGF-antagonist drug brolucizumab, marketed under the name "BEOVU." (CX-0329C; CX-0007.) BEOVU comes in two presentations for delivering the drug to a patient: a vial[50] and

[50] The vial presentation is supplied with a glass vial of BEOVU and a filter needle. (CX-0117C.0012.) A clinician withdraws the drug from the glass vial using the filter needle, removes the filter needle, and attaches an injection needle before injecting a patient. (*Id.* at 0004-0005.)

a prefilled syringe ("PFS").[51] (*Id.*) The vial presentation has already been approved by the FDA, and the PFS presentation is pending approval. (*Id.*) For the economic prong of domestic industry, Novartis relies primarily on investments in labor and capital related to research and development efforts for BEOVU, including clinical trials and the related FDA approval process. (CPreBr. at 49-54.)

Specifically, the evidence will show that Novartis has a Medical Affairs Team in the U.S. consisting of [redacted] employees. (JX-0424C, ¶9.) These employees have various medical and science backgrounds and are responsible for coordinating clinical trials and assessing the impact of data collected in those trials. (JX-0424C, ¶ 18, 22; JX-0405C, Tekker Tr., 50:4-51:9, 68:17-69:22, 98:2-99:6.) The evidence is expected to show that these employees spent [redacted] from 2018-2020[52] on BEOVU. (CX-0321C; CX-0325C.0017-19; JX-0424C, ¶ 21; CX-0234C.0039; Tekker Tr., 46:4-47:16, 68:4-69:22, 70:10-71:12.) The total compensation for these U.S.-based employees was [redacted] in 2018, [redacted] in 2019, and [redacted] for the first five months of 2020. (CX-0043C, ¶ 8.)

The evidence is expected to show that Novartis also employs approximately [redacted] full-time equivalent ("FTE") clinical development employees that perform work related to ongoing clinical studies for BEOVU in the United States. (JX-0424C, ¶¶

[51] As explained above, the BEOVU PFS practices various claims of the '631 patent. (*See* Section IV.C.)

[52] Novartis presents data for 2020 up to June 2020 when the Complaint was filed. Thus, unless otherwise noted, any reference in Section V of this brief to investments in 2020 refers to investments up to the filing of the Complaint.

22-23; JX-0105C.) The evidence is expected to show that these employees support Novartis's seven ongoing clinical trials for BEOVU, which are spread across at least 200 clinical sites in the U.S. (JX-0426C, ¶¶ 7-9; CX-0233.0004; JX-0409C, Wheeler Tr., 28:11-17, 29:6-20, 34:17-21; 38:1-39:12, 41:15-42:11, 44:16-45:9, 49:18-51:10; 59:7-65:4.) The total compensation for these U.S.-based employees was [redacted] in 2018, [redacted] in 2019, and [redacted] for the first five months of 2020. (CX-0043C, ¶¶ 5-7; CX-0043.0008-.0014; JX-0105C.)

Novartis also relies on its FDA regulatory affairs CMC team focused on BEOVU. (CPreBr. at 50.) The evidence is expected to show that these employees are responsible for various aspects of seeking FDA regulatory approval to market BEOVU in the U.S., including preparing the applications (*i.e.* the BLA and sBLA), preparing supporting documentation, and interacting with the FDA. (JX-0423, ¶¶9-19; JX-0401C, Dobres Tr., at 17:2-8, 35:16-36:6, 39:10-46:10.) The evidence is expected to show that the FDA regulatory affairs CMC team had between [redacted] U.S.-based team members during the relevant time. (JX-0423, ¶¶10-12; Dobres. Tr., 33:18-34:9.) The evidence is expected to show that Novartis invested approximately [redacted] in salaries for these employees between 2018 and 2020. (CX-0043C, ¶ 9; *id.* at .0096-111.)

The evidence is also expected to show that Novartis employs approximately [redacted] U.S.-based sales and marketing employees focused on BEOUV. (CX-0268C; CX-0042C, ¶ 4; CX-0250C; CX-0251C.0003.) Novartis invested approximately [redacted] in salaries for these employees. The Staff notes that the header in

Novartis's brief refers to "Product Training and Education Personnel," but the body of the brief asserts that these employees work on "branding" and refers to them as a "brand team." (CPreBr. at 51.) The Staff thus interprets these employees as dedicated to sales and marketing activities.[53] The Commission has explained that "[w]hile marketing and sales activity, alone, may not be sufficient to meet the domestic industry test, those activities may be considered as part of the overall evaluation of whether or not a Complainant meets the economic prong." *Certain Solid State Storage Drives, Stacked Electronics Components, and Products Containing Same*, Inv. No. 337-TA-1097, Comm'n Op. at 22 (June 29, 2018). While the Staff thus believes that the activities of Novartis's branding team should be included in the analysis, the amount of investment (*i.e.* just over [redacted]) is too small to make any difference in the overall analysis.

The evidence will also show that Novartis makes certain capital investments in BEOVU clinical studies. (JX-0104C; CX-0267C; JX-0105C.) The evidence will show that these investments include scientific meeting costs, lab services, lab materials, drug substance cost, and drug product cost. (CX-0318C.0006; CX-0313C; CX-0254C.0015-17; CX-0314C; CX-0316C; CX-0317C; JX-0104C; CX-0267C.)[54]

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[53] *See also* CX-0042C, ¶ 4 (explaining that the Product Training & Education Team was involved in BEOVU related activities that include "forecasting to inform supply production, packaging development for both commercial and sample product, pricing planning, and product training").

[54] Regeneron argues that these investments impermissibly include the purchase of BEOVU. (*See infra.* at 144.)

Globally, these costs total approximately [redacted] for 2018-2020. (CX-0266C; CX-0267C.) The evidence is expected to show that approximately 57% of the study centers for these clinical studies are in the U.S. (JX-0426C, ¶¶ 12, 16.) Thus, the evidence is expected to show that, after allocation, Novartis invests approximately [redacted] in clinical studies in the U.S. (JX-0426C, ¶¶ 12, 16; CX-0266C; CX-0267C.)

B. Employment of Labor or Capital

1. Novartis's investments in labor and capital

Novartis's domestic investments in BEOVU identified above are summarized in the table below:

DI Investment in Labor and Capital	Total Allocated Amount From 2018-May 2020
Medical Affairs Personnel	[redacted]
Clinical Trial and Development Personnel	[redacted]
Clinical Trials Capital Investments	[redacted]
FDA Regulatory Affairs and CMC Personnel	[redacted]
Total	[redacted]

The Staff expects that Novartis's expert Mr. Christopher Bakewell will testify as to how he allocated the investments identified above to the protected articles.

For the Medical Affairs Personnel, Mr. Bakewell is expected to testify that he allocated the salary investments based on the testimony of Mr. Dhaval Desai and

Dr. Csilla Tekker, who explained that those employees spent [redacted] of their time on BEOVU prior to 2019, and [redacted] of their time on BEOVU after that time. (JX-0424C.)

Mr. Bakewell is further expected to testify that the investments in salary for the Clinical Trial Personnel were allocated based on Novartis employees' estimates that of the approximately [redacted] total U.S. employees in that function, [redacted] FTEs were focused on BEOVU trials. (JX-0424C, ¶¶ 22-23.) Mr. Bakewell is expected to testify that he allocated the capital investments in clinical trials based on the testimony of Novartis's Mr. James Wheeler, who identified the number of study centers for a particular clinical trial that were in the U.S. and outside the U.S. (JX-0426C, ¶¶ 12, 16.) Mr. Wheeler then used the percentage of study centers in the U.S. for a particular study to allocate the U.S.-only portion of the capital investments in each BEOVU clinical trial. (JX-0426C, ¶¶ 15, 17.)

Mr. Bakewell is expected to testify that he allocated the FDA Regulatory Affairs and CMC Personnel salaries based on estimates made by Meghan Brown and Robert Dobres of Novartis of the time those employees spent on BEOVU. (JX-0423C.)

In sum, the Staff expects the evidence to show that Mr. Bakewell's allocations are reasonable and appropriate to capture investments in the U.S. dedicated to BEOVU. Further, with respect to the precision of Mr. Bakewell's allocations, the Staff notes that the Commission does not necessarily require a "precise accounting" of investments, "as most people do not document their daily affairs in contemplation

of possible litigation." *See Certain Stringed Musical Instruments & Components Thereof*, Inv. No. 337-TA-586, Comm'n Op., 2008 WL 2139143, at *15 (May 16, 2008); *see also Certain Strontium-Rubidium Radioisotope Infusion Sys., & Components Thereof Including Generators*, Inv. No. 337-TA-1110, Init. Det., 2019 WL 8752806, *92 (Aug. 1, 2019) (credit certain investments where the precise allocation was not absolutely certain because an ALJ "need not calculate the amount to the penny") *unreviewed in relevant part* ("*Certain Strontium-Rubidium Radioisotope Infusion Sys.*"). The Staff does not believe the evidence will show that any under- or over-counting of Novartis's investments based on Mr. Bakewell's analysis would substantially change the relevant amounts.

Finally, in the Staff's view investments in clinical studies and FDA regulatory activities are investments that the Commission has previously credited as the basis for a domestic industry, and there is no reason to treat Novartis's investments differently. *See e.g. Certain Strontium-Rubidium Radioisotope Infusion Sys.,* *94-95 (crediting investments in efforts to seek FDA approval as exploiting the patented invention), *unreviewed in relevant part*; *Certain Purple Protective Gloves*, Inv. No. 337-TA-500, Order No. 17, 2004 WL 2330140, *5-6 (Sept. 23, 2004), *unreviewed* (including in a domestic industry "functions related to regulatory affairs and quality assurance, scientific affairs, clinical education, … , research and development, medical and scientific operations, …"); *Certain Diltiazem Hydrochloride & Diltiazem Preparations*, Inv. No. 337-TA-349, Init. Det., 1995 WL 945191, at * 167 (Feb. 1, 1995), *unreviewed in relevant part* (including investments

in research studies involving domestic industry pharmaceuticals, and investments in FDA regulatory approval processes).

2. Novartis's investments are significant

The evidence is expected to show that Novartis's approximately [redacted] investments in labor and capital are quantitatively and qualitatively significant. For example, while clinical trials are more expensive in the U.S. than outside the U.S., [redacted] of Novartis's clinical trial investments are in the U.S. (JX-0426C, ¶¶ 14-15, 17; CX-0840.) Similarly, Mr. Bakewell is expected to testify that Novartis's investments in BEOVU, on an average monthly basis, comprise approximately [redacted] of BEOVU's average monthly revenue from the relevant time period. (JX-0115; CX-0853.) Mr. Bakewell also notes that Novartis's BEOVU investments are significant compared to the relevant industry; whereas clinical trials that support FDA approval of a new drug cost an average of $19 million, and ophthalmology studies average approximately $50 million, Novartis has spent more than [redacted] on BEOVU trials in the U.S. (CX-0345; CX-0346.)

Finally, the evidence is expected to show that Novartis's investments are essential for the BEOVU product to be sold in the U.S. Beyond the legal requirement of obtaining FDA approval, the investments in clinical studies allow Novartis to improve the safety and efficacy of BEOVU, both of which are important factors to patients and doctors choosing a treatment, and thus essential when bringing a drug product to market. (JX-0424, ¶¶ 14, 19.)

3. Regeneron's arguments

Regeneron raises three primary arguments in opposition to the Novartis's domestic industry contentions: (1) that investments in the BEOVU vial presentation should not count towards Novartis's domestic industry investments (RPreBr. at 229-236); (2) that Novartis's investments are overly-inclusive (RPreBr. at 236-238); and (3) that Novartis's investments are not significant (RPreBr. at 239-241). For the reasons below, the Staff disagrees.

a. Investments in the BEOVU vial are investments in an article protected by the '631 patent

Regeneron argues that investments related to BEOVU in the vial presentation should not count towards Novartis's domestic industry investments because the '631 patent covers only BEOVU in the PFS presentation. (RPreBr. at 229-236.) The Staff's view is that the relevant question is whether investments in BEOVU in the vial presentation are investments "with respect to the article[] protected by the ['631] patent" as required by the statute. *See* 19 U.S.C. § 1337(a)(3). For the reasons below, the Staff believes that investments in BEOVU in the vial are investments "with respect to the article[] protected by the ['631] patent" and therefore the Commission should consider such investments as part of Novartis's domestic industry.

(1) Prior Commission decisions credit investments in "essential" components of the article covered by the patent, and where the investment is central to enabling exploitation of the patented domestic industry article.

In prior decisions, the "the Commission has credited domestic investments when they are made with respect to an essential, necessary, and/or integral part of the article covered by the patent claims and/or where the investment is central to enabling exploitation of the article covered by the patent claims." *Certain Magnetic Tape Cartridges & Components Thereof*, Inv. No. 337-TA-1058, Comm'n Op., 2019 WL 2635509, at *32 (Apr. 9, 2019) ("*Magnetic Tape Cartridges*"); *see also id.* at *34 ("The Commission has defined the domestic industry to include investments necessary to bring to market the patented technology as embodied in the asserted domestic industry products"). For example, in *Magnetic Tape Cartridges*, the Commission credited investments in unpatented IBM 3592 tape drives because the drives were necessary to exploit the patented IBM 3592 tape cartridges. *Id.* at *32. Putting it another way, the Commission found that "the tape drive is necessary to bring the patented technology to the consumer market." *Id.* at *35; *see also id.* at *36 (complainants are "entitled to rely on expenses that [are] needed to ensure that the patented articles could be used by consumers.")

In *Certain Video Game Sys. & Wireless Controllers & Components Thereof*, Inv. No. 337-TA-770, Comm'n Op., 2013 WL 12410036, at *42 (Oct. 28, 2013) ("*Video Game Sys.*"), the Commissions rejected the complainant's reliance on investments in a live-action attraction called "MagiQuest," where the patented

technology was limited to a "toy wand" used as part of the attraction. Although agreeing that in "certain circumstances, the realities of the marketplace require a modification of the principle that the domestic industry is defined by the patented article," the Commission found no evidence that the "realities of the marketplace" required an "elaborate amusement park attraction" in order to use or sell complainant's "toy wand" product. *Id.* at *40-42. The Commission determined that the complainant could at best rely on expenses relating to certain effects and the activities that coordinate the effects, which were "central to enabling [the complainant] to exploit the technology of the claimed toy wands." *Id.* at *43.

The *Certain Sleep-Disordered Breathing Treatment Systems and Components Thereof*, Inv. No. 337-TA-890, Init. Det. (Sep. 16, 2014) ("*Sleep-Disordered Breathing*") investigation presented both creditable and non-creditable investments in products other than the precisely claimed articles.[55] The Commission credited domestic investments in an unpatented S9 flow generator because the flow generator "is central to enabling [the complainant] to exploit the patented technology of the H5i humidifier" given that the humidifier "is designed to work only with the S9 flow generator," and some of the "H5i humidifiers are sold in a 'co-pack' with an S9 flow generator." *Id.* at 147. Notably, the Commission found that "[a]lthough the H5i humidifier is a distinct product that is sometimes sold

[55] The Commission did not review the ALJ's finding that the complainant had established the existence of a domestic industry under 19 U.S.C. §§ 1337(a)(3)(A) and (B). *See* Comm'n Op., at 45 n. 13 (Jan. 16, 2015).

separately, *it cannot function on its own, and cannot practice the claims . . . without an S9 flow generator*." *Id.* at 149 (emphasis added). Conversely, for other patents directed to respiratory masks, the Commission found that the S9 flow generator and H5i humidifier were "not central to enabling [complainant] to exploit the patented technology of its [respiratory] masks because these masks are compatible with other [flow generators] and humidifiers, and they are marketed and sold separately from [the S9 and H5i]." *Id.* at 147.

Finally, in *Certain Marine Sonar Imaging Devices, Including Downscan & Sidescan Devices, Prod. Containing the Same, & Components Thereof*, Inv. No. 337-TA-921, Comm'n Op., 2016 WL 10987364, at *39 (Jan. 6, 2016) ("*Marine Sonar Imaging Devices*") the complainant relied on labor and capital investments related to "software updates" used in the complainant's "head units." The "head units" needed to be combined with other components to practice certain dependent claims of the relevant asserted patent. *Id.* The ALJ had rejected the complainant's investments "based on evidence that the software updates can be used with the LSS-1 and other products, such as the LSS-2, and the fact that the head units do not on their own practice any claim of the" relevant asserted patent. *Id.* On review, the Commission reversed that determination, finding that the ALJ had erred by "requiring Navico to show that its domestic investment related to only the patented product." *Id.* at *39 n. 31. The Commission noted that "evidence that the complainant's domestic investment related to other [products] in addition to the alleged domestic industry product did "not diminish [the fact] that [complainant's]

investment is also with respect to the domestic-industry articles." *Id.* at *39 (quoting from *Certain Integrated Circuit Chips and Products Containing the Same*, Inv. 337-TA-859, Comm'n Op., 2014 WL 12796437, at *28 (Aug. 22, 2014)).

(2) Clinical studies of the drug substance in BEOVU presented in a vial are central to enabling Novartis to exploit the '631 patented invention.

Here, the relevant facts are not in dispute. The BEOVU vial and PFS presentations both contain the same drug substance, *i.e.* brolucizumab (CX-0329C; CX-0007), though it is only the PFS presentation that practices claims of the '631 patent (*see supra* at Section IV.C). The brolucizumab drug is required for the BEOVU PFS to meet the "VEGF-antagonist" requirement of the claims. (*Id.*) Therefore the "article[] protected by the patent" in this case is BEOVU PFS and BEOVU PFS could not be the "article[] protected by the patent" without brolucizumab. In other words, there would be no patented invention without brolucizumab. Brolucizumab is thus an "essential, necessary, and/or integral part of the article covered by the patent claims" and investments in brolucizumab should be credited to Novartis's domestic industry. *See Magnetic Tape Cartridges*, at *32. Much like the relationship between the patented "H5i humidifier" and unpatented "S9 flow generator" in *Sleep-Disordered Breathing*, the BEOVU PFS is sold with brolucizumab and needs the brolucizumab to practice the claims of the '631 patent. *See Sleep-Disordered Breathing*, at 149. Indeed, the argument is even stronger in this case than in *Sleep-Disordered Breathing* because BEOVU PFS is *always* sold with brolucizumab.

Further, the evidence is expected to show that the clinical studies of BEOVU in a vial were directed to FDA approval of the brolucizumab drug (the same drug that is in the PFS), and not the glass vial in which the brolucizumab was presented. (JX-0113C.0016.) And without FDA approval of brolucizumab, Novartis could not exploit the patented BEOVU PFS. Beyond the regulatory requirements of the FDA, clinical studies of BEOVU in the vial presentation are directed to improving the safety and efficacy of the brolucizumab drug, which are both central to bringing a drug to consumers (*i.e.* patients and doctors). (JX-0424, ¶¶ 14, 19.) Thus, just like the "tape drives" in *Magnetic Tape Cartridges*, the "effects" in *Video Game Sys.*, and the "S9 flow generator" in *Sleep-Disordered Breathing*, investment in brolucizumab presented in a vial are central to bringing to market the '631 patented technology as embodied in the BEOVU PFS. *See Magnetic Tape Cartridges*, at *34; *Video Game Sys.*, at *43, *Sleep-Disordered Breathing*, at 147.

Regeneron argues that BEOVU in the vial does not practice the patent and therefore investments in BEOVU should not be included in Novartis's domestic industry. (RPreBr. at 229-231.) As explained above, however, that fact alone is not dispositive of the Commission's analysis of "articles" under the statute. Regeneron relies heavily on the holding of *Certain Subsea Telecommunications Sys. & Components Thereof*, Inv. No. 337-TA-1098, Init. Det., 2019 WL 2296160 (Apr. 26, 2019) ("*Subsea Telecommunications Sys.*"). But the facts of that investigation are distinguishable. The complainant in *Subsea Telecommunications Sys.* relied on investments in the NuWave Optima system. *Subsea Telecommunications Sys.* at

*46. But the NuWave Optima system could be equipped with one of two modules, the AC400 or the AC100; only systems equipped with the AC400 allegedly practiced the asserted patent. *Id.* The ALJ characterized the issue in that case as whether "investments in a version of a product that is not protected by the asserted patent can be combined with investments in a version that allegedly is protected by the asserted patent." *Id.* at *49. And the ALJ determined that the answer was that such investments in a version of a product that is not protected by the patent could not be counted. *Id.* at *50-51.[56]

Regeneron attempts to analogize *Subsea Telecommunications Sys.* by characterizing BEOVU in the vial as a separate, non-practicing version of BEOVU PFS. But that analogy misconstrues the relationship between the two products and misconstrues the nature of the investments. The BEOVU PFS comprises, generally speaking, two components: the drug substance (brolucizumab) and the delivery mechanism (the PFS). The entire device is covered by the '631 patent, which requires a terminally sterilized PFS containing a VEGF-antagonist (*e.g.* brolucizumab). The clinical studies on which Novartis relies were clinical studies of brolucizumab, one of the two components of BEOVU PFS; those studies were not

[56] That determination was affirmed on Commission review. *See Certain Subsea Telecommunications Sys. & Components Thereof*, Inv. No. 337-TA-1098, Comm'n Op., 2019 WL 9596565, at *23 (Oct. 21, 2019)

focused on the glass vial delivery mechanism.[57] Thus, unlike *Subsea Telecommunications Sys.,* the investments at issue here (*i.e.* investments in clinical studies) are investments in a component of the patented article, not investments in a technical and economically separate version of the product. Putting it another way, Novartis cannot exploit the patented PFS without BEOVU (since BEOVU is necessary to practice the patent), but the complainant in *Subsea Telecommunications Sys.* could clearly exploit the NuWave Optima system without the patented AC400 card because the evidence showed they were exploiting versions of the NuWave Optima system with a non-patented AC100 module. *Subsea Telecommunications Sys.* at *51.

Regeneron also argues that BEOVU is not central to Novartis's exploitation of BEOVU PFS because the claimed PFS could be used with any VEGF-antagonist, citing to *Sleep-Disordered Breathing*, at 150. (RPreBr. at 233.) That argument again misconstrues the economic realities here. As the evidence above shows, Novartis has invested large amounts of money in BEOVU and developed a PFS delivery mechanism for BEOVU. The fact that (as a matter of patent law) the '631 patent's syringe could be used with other VEGF-antagonists, is not the relevant issue. The issue is whether Novartis has some way other than BEOVU of exploiting the PFS, and the evidence will show that it does not. In *Sleep-Disordered*

[57] As Novartis points out, the sBLA application for BEOVU PFS relies on the same clinical data about brolucizumab that Novartis submitted to support the BLA for BEOVU presented in the vial. (CPreBR. at 54; JX-0423C, ¶¶ 17-18.)

Breathing, the evidence showed that the complainants could exploit the patented masks by selling them for use with their competitor's flow generators because the masks needed only standard tubing to connect to any flow generator. *Sleep-Disordered Breathing*, at 150. Contrast that holding with the ALJ's analysis of the patented humidifier and un-patented flow generator, in which he found that:

> [W]hether the [unpatented] S9 [flow generator] requires the [patented] H5i [humidifier] is a distinct question from whether the H5i requires the S9. The relevant issue is whether the H5i humidifier can be used without an S9 flow generator, and I find that it cannot be used alone because it would not have a supply of power or air. The H5i humidifier is wholly dependent on the S9 flow generator, and the S9 is thus central to enabling ResMed to exploit the patented technology of its humidifier.

Sleep-Disordered Breathing, at 150. In the Staff's view, the more apt analogy to *Sleep-Disordered Breathing* is that BEOVU PFS is like the H5i humidifier, and cannot be used without BEOVU the drug, like the H5i humidifier could not be used without the S9 flow generator. Thus, BEOVU the drug is central to enabling Novartis to exploit the PFS technology.

Regeneron also argues that BEOVU in the vial can be sold separately from BEOVU PFS and therefore investments in the vial should not be considered a part of Novartis's domestic industry. (RPreBr. at 234-236.) The Staff disagrees. As the Commission explained in *Marine Sonar Imaging Devices*, "evidence that the complainant's domestic investment related to other [products] in addition to the alleged domestic industry product did "not diminish [the fact] that [complainant's] investment is also with respect to the domestic-industry articles." *Id.* at *39. Here, evidence that Novartis's investments in BEOVU presented in the vial relate to

BEOVU sold in the vial, do not diminish the fact that (as explained above), the investments in BEOVU are also investments with respect to the domestic industry article, *i.e.* BEOVU PFS.

Finally, Regeneron has also asserted that BEOVU is "wholly absent from the '631 patent." (RPReBr. at 234.) While it's true that BEOVU presented in the vial is not a patented article per se, as explained above it is an essential component of the patented article that is central to bringing BEOVU PFS to market. And the Commission in *Marine Sonar Imaging Devices* reversed the ALJ's determination that investments in "head units" would not count towards the complainant's domestic industry because those "head units" were not patented articles. *Marine Sonar Imaging Devices*, at *39.

Moreover, the Staff disagrees that the fact that neither "BEOVU" or "brolucizumab" is identified by name in the '631 patent has any legal relevance to the domestic industry inquiry. Regeneron does not dispute that BEOVU is a "VEGF-antagonist" and therefore meets the "VEGF-antagonist" limitation of the claims, whether the claims identify BEOVU by name or not. The Commission's domestic industry economic prong case law does not require that the trade name or product name of a domestic industry article (or component thereof) be identified by name in an asserted patent claim. Nor is that a requirement of the infringement analysis applied in the technical prong.

b. Novartis's investments are not overly inclusive

Regeneron also argues that Novartis's analysis includes improper investments. (RPreBr. at 236-238.)

First, Regeneron takes issue with investments included in Novartis's clinical trial costs as not reflective of investments in "capital." The Staff disagrees that *Lelo Inc. v. International Trade Comm'n*, 786 F.3d 879, 883-85 (Fed. Cir. 2015) "defined" the term "capital" as used in Section 337 to mean only 'a stock of accumulated goods'" or "capital investments in domestic facilities." The court in *Lelo* was using the definition of "capital" as part of a larger explanation for why the "plain text of § 337 requires a quantitative analysis" of whether investments are significant. *Lelo*, at 786 F.3d at 883. Nothing in *Lelo* purported to overturn or redefine what investments the Commission considers "capital." And as explained above, the Commission has previously included such investments in clinical studies required for FDA approval in its domestic industry analysis, and the Staff sees no reason to treat Novartis's investments any differently. (*See supra* at 140.)

Second, Regeneron argues that some unspecified portion of the capital investments are for [redacted] and thus should not count towards Novartis' domestic industry. (RPreBr. at 236-237.) The Staff notes that the evidence on which Regeneron relies (testimony from Novartis's Mr. James Wheeler), is somewhat ambiguous on whether the drug purchases were for BEOVU or other drugs that BEOVU is compared to. Moreover, evidence cited by Novartis indicates that the cost is to

purchase the comparator drugs, such as EYLEA. (*See e.g.* CX-0313C.) The Staff intends to explore this question with Novartis's witnesses at the hearing.

Third, Regeneron argues that Novartis's investments include investments in products other than BEOVU. (RPreBr. at 237.) This appears to relate to a discrepancy between the originally cited declaration of Mr. Dhaval Desai (JX-0424C), and the testimony of his replacement witness, Ms. Csilla Tekker, regarding the amount of time the medical affairs personnel spent on BEOVU after 2019. Although Regeneron is correct that Ms. Tekker explained that after 2019 the medical affairs personnel spent only [redacted] of their time on BEOVU, it is unclear to the Staff how that makes any substantive difference in the overall analysis, nor does Regeneron provide any explanation. As noted above, the Commission does not necessarily require a "precise accounting" of investments, "as most people do not document their daily affairs in contemplation of possible litigation." *See Certain Stringed Musical Instruments & Components Thereof*, Inv. No. 337-TA-586, Comm'n Op., 2008 WL 2139143, at *15 (May 16, 2008).

Fourth, Regeneron appears to argue that it was improper for Novartis to rely on investments going back to 2017, only three years before the filing of the Complaint. (RPreBr. at 237.) But Commission precedent has long held that a complainant can rely on past investments where the investments are on-going. *See e.g. Certain Electronic Digital Media Devices and Components Thereof*, Inv. No. 337-TA-796, Comm'n Op., at 99-100 (Sep. 6, 2013). Regeneron does not argue that

Novartis had stopped investing in BEOVU as of the filing of the Complaint.[58] Therefore, Regeneron is wrong that Novartis cannot rely on investments going back to 2017.

c. Novartis's investments are significant

As explained above, the Staff's view is that the evidence will show that Novartis's investments are significant. In opposition to that position, Regeneron repeats the same arguments that investments in BEOVU the drug substance should not be counted, and that investments in clinical studies in support of FDA approval should not count unless they involve domestic manufacturing. For the reasons already explained above, the Staff disagrees. Additionally, the Staff notes that it should be considered "black letter" Commission law at this point that domestic industry investments do not require manufacturing. *See Certain Robotic Vacuum Cleaning Devices and Components Thereof Such as Spare Parts*, Inv. No. 337-TA-1057, Comm'n Op., at 11-12 (Aug. 1, 2018) (explaining prior Commission decisions finding that the "statutory text of section 337 does not limit sections 337(a)(3)(A) and (B) to investments related to manufacturing or any other type of industry").

Regeneron also argues that because Regeneron invested more in EYLEA than Novartis asserts it has invested in the U.S. for BEOVU, Novartis's investments are not significant. (RPreBr. at 240.) But Regeneron is not performing

[58] As noted above, the evidence is expected to show that Novartis's investments are on-going.

an apples to apples comparison by comparing the cost to develop and manufacture EYLEA to the cost for clinical trials and regulatory approval for BEOVU. Rather, a better comparison is Regeneron's assertion that it spent "[redacted] in clinical trials and regulatory work." (*Id.*) The cited evidence for that assertion, paragraph 67 of Dr. Kaplan's rebuttal report, asserts Regeneron spent [redacted] on clinical trials and regulatory affairs. (JX-0441C.0024.) Given that [redacted] than the [redacted] that Novartis asserts that Novartis has invested in clinical trials and regulatory affairs, the Staff's view is that such a comparison supports (rather than disproves) the significance of Novartis's investments.

Regeneron also argues that Novartis's investments are not significant because Novartis did not compare its foreign expenditures to its domestic expenditures. (RPreBr. at 241.) But comparing a complainant's domestic expenditures to its foreign expenditures is only one of the possible factors that the Commission could, but is not required to, consider in assessing a domestic industry. *Certain Printing and Imaging Devices and Components Thereof*, Inv. No. 337-TA-690, Comm'n Op., at 27-28 (Nov. 2011).

Finally, Regeneron argues that Novartis's investments are not significant because BEOVU is not on sale and it is [redacted] (RPreBr. at 241). First, there is no requirement that the "articles protected by the patent" be commercially available articles. The Commission has rejected the notion that the "article protected by the patent" "must

be a product that came to market, or is expected to come to market, under the protective umbrella of the asserted patent that the product commercializes." *See Certain Computers & Computer Peripheral Devices, & Components Thereof, & Prod. Containing Same*, Inv. No. 337-TA-841, Comm'n Op., 2014 WL 5380098, at *24 (Jan. 9, 2014); *see also Certain Non-Volatile Memory Devices & Prod. Containing the Same*, Inv. No. 337-TA-1046, Comm'n Op., 2018 WL 6012622, at *25 (Oct. 26, 2018) ("The term 'article' on its own is sufficiently capacious to embrace pre-commercial or non-commercial items") ("*Non-Volatile Memory Devices*"); *Certain Digital Cameras, Software, & Components Thereof*, Inv. No. 337-TA-1059, Init. Det. (Aug. 17, 2018), *terminated prior to Commission review* ("Commission precedent does not support the legal requirement that [respondents] espouses: that 'articles' be 'production ready'"). The fact that BEOVU PFS has not been approved by the FDA does not take away from Novartis's significant investments. *See e.g. Certain Strontium-Rubidium Radioisotope Infusion Sys.*, 2019 WL 8752806, at *88-90 (finding that investments in articles that "exist in the United States that embody the claims of the asserted patents" should be credited towards a domestic industry even where articles had yet to be approved by the FDA).

Second, Regeneron's concern is speculative. The only evidence that Regeneron puts forward to suggest that BEOVU PFS [redacted] was evidence related to alleged safety issues with the underlying drug substance in BEOVU. (JX-0407C, 128:10-18.) But that drug substance has already been approved by the FDA (CX-0007), and it does not appear

that any of the alleged issues led to a withdrawal of the FDA's approval. The Staff is not aware of any evidence that contradicts Novartis's contention that [redacted].

Third, even assuming for the sake of argument that there is a substantive [redacted], the Staff does not believe that fact would justify a finding that Novartis does not meet the domestic industry requirement. Rather, to the extent a violation is found and a limited exclusion order issues, and if the FDA ultimately does not approve BEOVU PFS, Regeneron can petition the Commission for modification or recission of the exclusion order under Commission Rule 210.76. *See* 19 C.F.R. § 210.76; *see also Non-Volatile Memory Devices*, at *31 n. 15 ("The Commission notes that should there be changed circumstances as to the status of [complainant's] domestic industry in the process of being established, for example, should [complainant] cease its efforts to establish such an industry, [respondent] can petition the Commission to modify the remedial orders under 19 C.F.R. § 210.76.")

C. Novartis Has Not Made Substantial Investment in Exploitation of the '631 Patent

Novartis relies on the same investments under subparagraph (C) as it does for labor and employment under subparagraph (B). (CPreBr. at 54.) In the Staff's view, however, Novartis will not be able to show sufficient evidence of a nexus between the '631 patent and investments in BEOVU in the vial. Moreover, when

considering only Novartis's investments in the PFS, the Staff believes the evidence will show that such investments are not substantial.

1. Lack of nexus

The Commission has explained that "under subparagraph (C), the complainant must establish that there is a nexus between the claimed investment and the asserted patent. *See Certain Integrated Circuit Chips*, 2014 WL 12796437, at *22. "To the extent that the Patented technology arises from endeavors in the United States, such a nexus would ordinarily exist." *Id.* at *23. Additionally, the "nexus may readily be inferred based on evidence that the claimed investment is in the domestic industry article, which itself is the physical embodiment of the asserted patent." *Id.* at *23. But "exploitation" is a "generally broad term that encompasses activities such as efforts to improve, develop, or otherwise take advantage of the asserted Patent." *Id.* at *23.

Here, the evidence will show that the PFS technology of the '631 patent arose from the inventors' efforts outside the U.S.[59] Moreover, the evidence is expected to show that Novartis's investments are in BEOVU presented in the vial, which is not the "physical embodiment" of the asserted patent. (CPreBr. at 54.) In the Staff's view, efforts to improve the safety and efficacy of the BEOVU drug substance are not efforts to improve, develop, or otherwise take advantage of the '631 patent's claimed PFS. The evidence is not expected to show that the clinical studies of

[59] For example, the named inventors are identified on the face of the '631 patent as being located in Germany, Switzerland, and France. ('631 patent, cover page.)

BEOVU presented in the vial led to any improvements in, for example, the amounts of silicone in a PFS or the proper break loose force for a PFS. (CPreBr. at 55 ("While preparing for FDA approval and launch of BEOVU PFS, Novartis has engaged in significant research and development to improve the safety and efficacy of BEOVU, especially through critical scientific work on the VEGF-antagonist active ingredient").)

It is true that the claims of the '631 patent require a VEGF-antagonist and that BEOVU is one such VEGF-antagonist. Viewed in the proper context, however, the Staff does not believe that fact shows the existence of a nexus. Novartis does not dispute that the '631 patent is directed to a novel syringe, not a novel drug. (CPreBr. at 178 ("The Patent claims a medical device for injecting a VEGF antagonist, and the specification enables and describes that device").) The claims of the '631 patent, moreover, broadly claim a "VEGF-antagonist"; although BEOVU meets that limitation, so do many other drugs, including drugs like Macugen or Lucentis that were indisputably known prior to the invention of the '631 patent. (JX-0005C; JX-0303; RX05030.) In other words, the '631 patent is not specifically concerned with improved "VEGF-antagonists" but instead is directed to an improved syringe that is designed to work with any "VEGF-antagonist" including those know in the prior art. (CPreBr. at 178.) Viewed in that light, the Staff does not believe investments in the BEOVU drug substance are sufficiently related to exploitation of the novel syringe invention of the '631 patent.

As explained above, in the context of subparagraph (B) the Staff does not view it as significant that investments in BEOVU the vial related to both the vial presentation that is sold to consumers, as well as the patent-protected PFS presentation that is pending FDA approval. *See Certain Integrated Circuit Chips*, at *28 ("In particular, the Respondents argue that Realtek's domestic investment relates not only to the chips put forward as domestic industry articles here, but also to other chips. That fact does not diminish that Realtek's investment is also with respect to the domestic-industry articles"). But here, the fact that the BEOVU vial is currently sold by Novarits as a product that does not use the patented PFS, "negat[es] a possible inference that the R&D" related to BEOVU in the vial "was in exploitation of the patented invention as embodied in the" BEOVU PFS. *Id.* at *26.

The difference, in the Staff's view, reflects a difference in the statutory requirements of subparagraphs (B) and (C); Novartis may be able to show that it's investing in labor and capital relating to investments in an article protected by the '631 patent, but Novartis will not be able to show a sufficient nexus between investments in BEOVU in the vial and investments in the patented PFS technology.

2. Investments not substantial

Novartis does not appear to assert that investments that are directed only to the PFS are substantial (or significant). To the extent the issue is raised, however, the evidence is expected to show that such investments only sum up to approximately [redacted] (JX-0432C, at ¶¶ 142-143.) In the Staff's view, such a sum

is clearly not quantitatively substantial, at least because it is less than [redacted] of the [redacted] that Novartis invested in research and development of BEOVU.

VI. PUBLIC INTEREST

A. Legal Standards

Section 337 defines a two-stage process for the Commission to act upon a complaint. The Commission first "determines, as a result of an investigation under this section" whether "there is a violation of this section." *See* 19 U.S.C. § 1337(d)(1). If the Commission determines a violation has occurred, the Commission "shall direct that the articles concerned . . . be excluded from entry into the United States unless after considering the effect of such exclusion" on four public interest factors the Commission determines a remedy should not issue. *Certain Magnetic Tape Cartridges and Components Thereof*, Inv. No. 337-TA-1058, Comm. Op. at 67 (Apr. 9, 2019) (original emphasis omitted). Those four public interest factors are: (1) the public health and welfare; (2) the competitive conditions in the United States economy; (3) the production of like or directly competitive articles in the United States; and (4) the United States consumers. *Id.*

As a general matter, the Commission has frequently explained that "[t]he public interest favors the protection of U.S. intellectual property rights by excluding infringing imports." *Certain Magnetic Data Storage Tapes and Cartridges Containing the Same (II)*, Inv. No. 337-TA-1076, Comm. Op. at 64 (Jun. 20, 2019) (citing *Certain Two-Handle Centerset Faucets & Escutcheons, & Components Thereof*, Inv. No. 337-TA-422, Comm'n. Op., at 9 (Jul. 21, 2000)).

But the Commission has denied an exclusionary remedy or has tailored its relief in light of the statutory public interest factors when the circumstances of a particular investigation require it. *See, e.g., Spansion, Inc. v. U.S. Int'l Trade Comm'n*, 629 F.3d 1331, 1360 (Fed. Cir. 2010) (discussing historical application of the public interest factors); *Certain Microfluidic Devices*, Inv. No. 337-TA-1068, Comm. Op., at 1, 22-48, 53-54 (Jan. 10, 2020) (analyzing the public interest, discussing applicable precedent, and ultimately issuing a tailored LEO and a tailored CDO); *Certain Road Milling Machines & Components Thereof*, Inv. No. 337-TA-1067, Comm. Op., at 32-33 (Jul. 18, 2019) (exempting service parts); *Certain Personal Data and Mobile Communication Devices and Related Software*, Inv. No. 337-TA-710, Comm'n Op., 83 (Dec. 29, 2011) (delaying the effective date of an exclusion order based on competitive conditions in the U.S. economy); *Certain Baseband Processor Chips and Chipsets, Transmitter and Receiver (Radio) Chips, Power Control Chips, and Products Containing Same, Including Cellular Telephone Handsets*, Inv. No. 337-TA-543, Comm. Op., at 148–54 (June 19, 2007) (grandfathering certain existent mobile telephone models from the scope of the exclusion order); *Certain Automated Mechanical Transmission Systems for Medium-Duty and Heavy-Duty Trucks, and Components Thereof*, Inv. No. 337-TA-503, Comm. Op., at 5 (May 9, 2005) (exempting from the scope of the exclusion order replacement parts for existing truck transmissions); *Certain Sortation Systems, Parts Thereof, and Products Containing Same*, Inv. No. 337-TA-460, Comm. Op., at

18–20 (Feb. 19, 2003) (exempting from the scope of the exclusion order replacement parts for a UPS hub facility).

The Commission has also issued delays of its exclusion orders when the circumstances warrant. *See Certain Lithium Ion Batteries, Battery Cells, Battery Modules, Battery Packs, Components Thereof, and Processes Therefor*, Inv. No. 337-TA-1159, Comm'n Op., at 77-79 (Mar. 4, 2021) (granting two and four year exemptions to the exclusion order with respect to two third party automotive makers to provide sufficient time to source alternatives to the excluded batteries) ("*Certain Lithium Ion Batteries*"); *Certain Personal Data and Mobile Communication Devices*, at 79-81 (providing a transition period of four months to telephone carriers to obtain alternative Android smartphones); *see also Certain Strontium-Rubidium Radioisotope Infusion Sys.,* 2019 WL 8752806, at *111 (recommending 12-month delay of exclusion order to allow health care providers to switch to non-infringing alternative and "maintain the standard of care for their current patients without interruption").[60]

There have also been a few instances when public interest considerations have prevented the Commission from issuing a remedy. *See Certain Automatic Crankpin Grinders*, Inv. No. 337-TA-60, Comm. Det. & Order at 2, USITC Pub. No.

[60] In the 1110 Investigation the Commission affirmed the ALJ's finding of no violation of section 337 on the basis that the asserted patents were invalid. *See Certain Strontium-Rubidium Radioisotope Infusion Systems,* Comm'n Op., at 1 (Dec. 11, 2019). The Commission thus did not address the ALJ's recommendations on remedy or the public interest.

1022 (1979) (overriding national policy in increasing supply of fuel-efficient automobiles; domestic industry unable to supply U.S. demand); *Certain Inclined Field Acceleration Tubes*, Inv. No. 337-TA-67, Comm. Op. at 21-31, USITC Pub. No. 1119 (1980) (overriding public interest in continuing basic atomic research with imported acceleration tubes deemed to be of higher quality than domestic product); *Certain Fluidized Supporting Apparatus*, Inv. No. 337-TA-182/188, Comm. Op., 1984 WL 63741, at *10-11 (Oct. 1984) (relief denied where products provide benefits unavailable from any other device or method and domestic producer could not meet demand for hospital beds for burn patients) ("*Burn Beds*").

In the three instances where the Commission has found a public interest impact significant enough to deny relief, "the exclusion order was denied because inadequate supply within the United States—by both the patentee and domestic licensees—meant that an exclusion order would deprive the public of products necessary for some important health or welfare need." *Spansion*, 629 F.3d at 1360.

B. Analysis

In the Staff's view, the evidence will show that there is significant risk that issuance of remedial orders in this case would impact the public health and welfare due to an [redacted] For the same reasons, the Staff believes the evidence will show that remedial orders may risk harm to U.S. consumers who are being treated with anti-VEGF drugs. Therefore, as explained below, the Staff believes the Commission should tailor any exclusion orders to provide a delay of [redacted] for Regeneron to [redacted] of EYLEA in the vial to replace the

excluded EYLEA PFS. In the alternative, the record contains evidence that may support the complete denial of exclusionary relief based on [redacted] when using the vial presentation of EYLEA as compared to the PFS presentation.

1. Effect on public health and welfare

Regeneron puts forward two distinct reasons that an exclusion order will negatively impact the public health and welfare: (a) there will be [redacted] of EYLEA in the vial to replace the excluded EYLEA PFS (RPreBr. at 255-262), and (b) the alternatives to EYLEA PFS are all inferior (RPreBr. at 262-279).[61] The Staff addresses the supply argument and the alternatives argument separately below.

a. The supply argument

The Staff believes the evidence will show that there is a significant risk that an exclusion order would result in [redacted] anti-VEGF treatments, which would pose a severe risk to public health and welfare First, Regeneron may not have [redacted]. Second, even with [redacted], Regeneron may not be able to [redacted]. Third, even with [redacted], Regeneron may be [redacted]. And fourth, there is no evidence that any alternative

[61] Although neither of the private parties' briefs structure the arguments around the four statutory categories, the Staff's understanding is that the arguments are largely, if not solely, directed towards the impact of a potential exclusion order on the public health and welfare.

supply of ant-VEGF treatments will be available in [redacted] caused by excluding EYLEA PFS.

(1) Estimated expected [redacted]

Based on the current target date, any exclusion order in this investigation would take effect on November 29, 2021, though Regeneron could continue to import EYLEA PFS under bond until January 28, 2022, when the Presidential review period expires. The evidence is expected to show that Regeneron forecasts that it will need to provide U.S. patients with approximately [redacted] doses of EYLEA (vial and/or PFS) in 2022. (JX-0382C; JX-0384C.) Novartis does not appear to contest this forecast. Assuming no exclusion order, Regeneron currently forecasts that [redacted] of those doses (about [redacted] will be the PFS presentation and [redacted] (about [redacted]) will be the vial presentation. (JX-0382C.) Again, Novartis does not appear to contest this forecast. Regeneron reports that it currently has approximately [redacted] filled vials in inventory, of which all but [redacted] by the end of 2021.[62] (JX-0410C, Walsh Tr., at 150:1-151:6; RX-0834C.) Given that inventory level, Regeneron will need to make [redacted] vials to supply the currently expected vial demand in 2022.

Thus, after the exclusion order goes into effect in January 2022, Regeneron will need to replace an expected [redacted] units of EYLEA PFS with [redacted] units of EYELA in the vial during 2022 (and presumably similar or greater amounts

[62] A single vial is a single dose of medicine. (*See e.g.* CX-0491C.0005 (FDA-approved prescribing information noting that vial is a "single-dose vial").)

in the following years). Compared to the currently expected demand of [redacted] vials, that's an increase of approximately [redacted] vials, *i.e.* an approximately [redacted] increase in the amount of EYLEA vials Regeneron may need to provide in 2022.

In the Staff's view, the relevant question is therefore whether the evidence shows that the market[63] will be able to supply the equivalent of the excluded [redacted] doses of EYLEA PFS, and if not, what would be the impact on public health and welfare.

(2) Impact of a [redacted]

The accused EYLEA products are indicated for the treatment of three of the most common VEGF-related eye diseases: wet age-related macular degeneration ("wet AMD"), diabetic retinopathy ("DR"), diabetic macular edema ("DME"), and macular edema following retinal vein occlusion ("MEfRVO"). (JX-0259C.0005.) The testimony of Regeneron's expert Dr. Szilard Kiss is expected to show that if left untreated, these conditions result in vision loss, including potential severe vision loss or even blindness. (CX-0007.0004, Novartis press release re FDA approval of BEOVU ("Wet AMD distorts central vision and ultimately causes blindness and loss

[63] As explained below, the only reasonably available FDA-approved alternative to EYLEA is Lucentis from Novartis's licensee Genentech because BEOVU is not indicated for the same conditions and there is also no evidence it can be supplied in sufficient quantities to replace the excluded EYLEA PFS. Effectively then, the relevant market is Genentech and Regeneron.

of independence").) For example, the evidence is expected to show that wet AMD is the leading cause of vision loss in older Americans. (RX-0923.)

Dr. Kiss is expected to testify that unlike the earlier available Macugen PFS, more recent anti-VEGF treatments like Lucentis and EYLEA are effective in not only preventing the vision loss caused by the above conditions, but in many cases restoring lost vision. (JX-0372.) None of the currently available anti-VEGF drugs are a cure for the indicated eye diseases and these treatments all require treatment for the lifetime of the patient. (JX-0445, ¶ 33.) As a logical consequence of this fact, discontinuing treatment allows the disease to resume its natural progression and leads ultimately to vision loss.

The evidence is expected to show that studies have found that missing a regularly scheduled injection can lead to vision loss.[64] (JX-0500; JX-0470; JX-0389; RX-0900; JX-0388; RX-0909.0013; JX-0530.) Both Novartis's expert Dr. Calman, and Regeneron's expert Dr. Kiss are expected to testify that if patients go without treatment for long enough, any vision loss may become permanent even if the interrupted anti-VEGF treatment resumes.

Thus, in the Staff's view, any question about the risk of a [redacted] must be weighed against the potential severe impact on public health should such a [redacted] occur, *i.e.* patients may suffer either temporary or permanent vision loss, up to and

[64] Dr. Kiss is expected to testify that the precise treatment interval differs from patient to patient. EYLEA's label recommends that it be given monthly for the first three months, then bi-monthly after that. (JX-0259C.0005.)

including blindness, because they are unable to obtain the relevant anti-VEGF drugs.

(3) Drug manufacturing

The evidence is expected to show that there is a reasonable risk that Regeneron [redacted] The vials have a "target fill volume" of [redacted] of drug substance, while the PFS presentation volume is [redacted]. (RX-0763C.) Based on the forecasts identified above, if there is no exclusion order Regeneron would need to make approximately [redacted] of drugs substance for expected PFS doses, and [redacted] for the expected vial doses, or a total of approximately [redacted] of drug substance. If Regeneron is required to supply the same number of doses only in a vial, it will need to manufacture [redacted] of drugs substance, *i.e.* about a [redacted] over the currently projected amount.

Regeneron's witnesses are expected to testify that Regeneron would be [redacted] by that amount without [redacted].[65] (JX-0413C, Grimaldi Tr., at 116:4-118:2; 109:9-114:6; Walsh Tr., at 161:6-162:14; JX-0406C, Van Plew Tr., 227:6-229:5, 230:18-233:12.) Moreover, the evidence is expected to show that Regeneron would need between [redacted]

[65] Regeneron's Pre-Hearing Brief identifies these drugs and their indications at RPreBr. at 256 n. 72.

[redacted] (Grimaldi Tr., 112:1-10; RX-0775.0025-26.) For example, Regeneron's supply chain expert, Mr. George Serafin, is expected to testify that [redacted] (JX-0421C.0036-37.) Designated deposition testimony from Ms. Walsh is also expected to explain that [redacted] (Walsh Tr., 161:6-16.) Thus, even if Regeneron had [redacted] in required drug supply in the U.S.

In reply, Novartis asserts that because Regeneron supplied the market with the vial only presentation "just 12 months ago," it should have no trouble switching back to the vial now. (CPreBr. at 206.) But that argument incorrectly assumes that [redacted] According to Regeneron's documents, Regeneron supplied approximately [redacted] PFS doses and [redacted] vial doses in 2019. (JX-0382C.) That is approximately [redacted] of drug substance. Thus, even assuming for the sake of argument that Regeneron's 2019 production levels [redacted] Moreover, the Staff notes that in the time period that Novartis points to (2019), Regeneron experienced [redacted] in demand for the drug substance

of approximately [redacted] (from 2018 to 2019) (JX-0384C; JX-0382C) and [redacted] from 2019 to 2020 [redacted] (JX-0382C).[66] In the Staff's view, that supports Regeneron's assertion that it would [redacted] for the drug substance in 2022, because the data does not provide any indication that Regeneron has needed to meet that sort of spike in demand in recent years.

Novartis also asserts that "Regeneron has publicly touted the speed and flexibility of its drug manufacturing process for quickly re-tooling its manufacturing lines," quoting a news article in which a Regeneron executive touts the fact that the company was able to shift its production to produce additional COVID-19 antibody cocktail in response to the COVID-19 pandemic. (CPreBr. at 207; CX-1311; CX-1272.) The Staff understands this argument to posit that because Regeneron could quickly shift the capacity the Regeneron has developed over the last year to manufacture the COVID-19 antibody cocktail, Regeneron would be able to shift back to the production of EYLEA. The Staff disagrees that this argument, even if true as a factual matter, negates the public interest concern. [redacted] of the COVID-19 cocktail to [redacted] seems, to the Staff, to be facially bad for the public health and welfare given the scope and severity of the COVID-19 pandemic.

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66 [redacted]

Novartis similarly characterizes the increase in production to supply sufficient EYLEA vials as an "inconvenience" only (CPreBr. at 207), but the cited testimony from Ms. Walsh of Regeneron merely explains that [redacted] (Walsh Tr., 160:17-161:5.) In the Staff's view, the cited testimony does not explain whether Regeneron [redacted] in 2022.

The Staff understands Novartis's position to be that it would not impact the public health or welfare for Regeneron to [redacted] But Novartis presents no evidence to show that [redacted] of the various other drugs that Regeneron sells, *e.g.* to treat COVID-19, eczema, cardiovascular disease, and skin cancer,[67] would not impact the public health or welfare. Such an analysis would seem to invite a secondary inquiry into whether sufficient replacements exist for those drugs. In the Staff's view such a secondary inquiry would be an unnecessary distraction (and there is insufficient evidence regarding those questions in the record). Rather, the Staff's view is that Novartis effectively concedes that [redacted] that Regeneron makes, Novartis has no affirmative evidence to show that Regeneron would be able to [redacted] EYLEA drug substance than it is currently planning to make to supply the U.S. market in 2022 (and beyond).

[67] RPreBr. at 256 n. 72.

(4) [redacted]

The evidence is expected to show that there is a reasonable risk that Regeneron [redacted] to replace the excluded EYLEA PFS with the vial presentation. Testimony from Regeneron's witnesses is expected to show that Regeneron has [redacted] (JX-0382C.) As explained above, in 2022 when an exclusion order went into effect, [redacted]

Novartis's "first" and "second" arguments regarding the [redacted] are that there is no global shortage of glass vials or evidence that COVID-19 has caused such a shortage. (CPreBr. at 202-203.) The Staff agrees that the evidence put forward by Novartis suggests that to the extent any shortage of glass vials exists currently due to the pandemic, it will likely be resolved by 2022. (CPReBr. at 202 n. 104.)

The Staff notes, however, that some of evidence points to continued issues for mid-sized companies like Regeneron. Specifically, an executive at Corning explained in a September 2020 article regarding possible vial shortages due to the pandemic, that large companies with glass contracts in place "should be fine" but "small-to-mid-sized companies" would find it "much more difficult" to secure glass vials if "they don't have existing supply agreements." (CX-1271.0007.) But the executive noted that any supply constraints should be resolved within "12 to 18 months." *i.e.* by the end of 2021, and that increases in capacity at vial manufactures might lead to an excess of supply. (*Id.* at 0011.)

Novartis's "third" argument is that [redacted] in the event of an exclusion order. (CPreBr. at 203-204.) In the Staff's view, this argument is contrary to Commission case law because it assumes either (or both) that (a) a respondent named in a section 337 investigation is under a legal duty to remediate the effect of a potential exclusion order during the pendency of an investigation, and/or (b) that the actions of a respondent during the pendency of an investigation are relevant to whether the Commission's issuance of an exclusion order will impact the public health and welfare.

As to (a), Novartis argues several times that there will be no public interest concerns if Regeneron takes action now to [redacted] (CPreBr. at 204, 210-215.) But the Staff is not aware of any statute, Commission rule, or caselaw that requires a respondent named in a section 337 section investigation to remediate the negative impact of a potential exclusion order on the public interest

prior to the finding of a violation by the Commission. By statute, the obligation of considering whether an exclusion order will impact the public interest falls on the Commission, and it is only required to make that determination after it has determined that a violation has occurred. *See* 19 U.S.C. § 1337(d)(1) ("If the Commission determines … that there is a violation of this section, it shall direct that the articles concerned … be excluded from entry into the United States, unless, after considering the [public interest factors], it finds that such articles should not be excluded from entry.")[68] Nothing in the statute requires a respondent to take action to address potential public interest impacts prior to the finding of a violation. Similarly, a respondent named in a section 337 investigation is not assumed to be in violation merely by being named as a respondent, and thus is not required to take action to remediate the impact of a potential exclusion order prior to the conclusion of the Commission's investigation. Although taking such action might be a prudent business decision, it is not a legal requirement for respondents appearing in section 337 investigations at the Commission.

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[68] The legislative history regarding the addition of the "public interest" factors also shows that the obligation falls on the Commission to consider the public interest before issuing exclusion order. *See* S. REP. 93-1298, 1974 U.S.C.C.A.N. 7186, 7326 ("However, before ordering exclusion or issuing a cease and desist order, the Commission would be required to consider the effect of such action upon the public health and welfare, competitive conditions in the U.S. economy, the production of like or directly competitive articles in the United States, and U.S. consumers. The Committee feels that the public interest must be paramount in the administration of this statute.")

As to (b), Novartis's argument also implies that the Commission should decline to delay the exclusion order here if the Commission finds that Regeneron [redacted] In the Staff's view, that is both contrary to the letter and spirit of the statue. Under the statute the Commission must "consider[] the effect of [an exclusion order] upon the public health and welfare" (*see* 19 U.S.C. § 1337(d)) and determine whether it should decline to issue such an order based on that consideration. Nothing in the text suggests the Commission should or must include in that inquiry a determination of what actions the respondents took during the pendency of the investigation to remediate any public interest concerns. Moreover, the Staff believes it would be contrary to the spirit of the statute for the Commission to determine, for example, that an exclusion order would have a severe negative impact on the public health and welfare but that the exclusion order should issue anyway because a respondent failed to take remedial action during the pendency of the investigation. That would in effect make the public health and welfare pay the price for some perceived failure of a respondent.

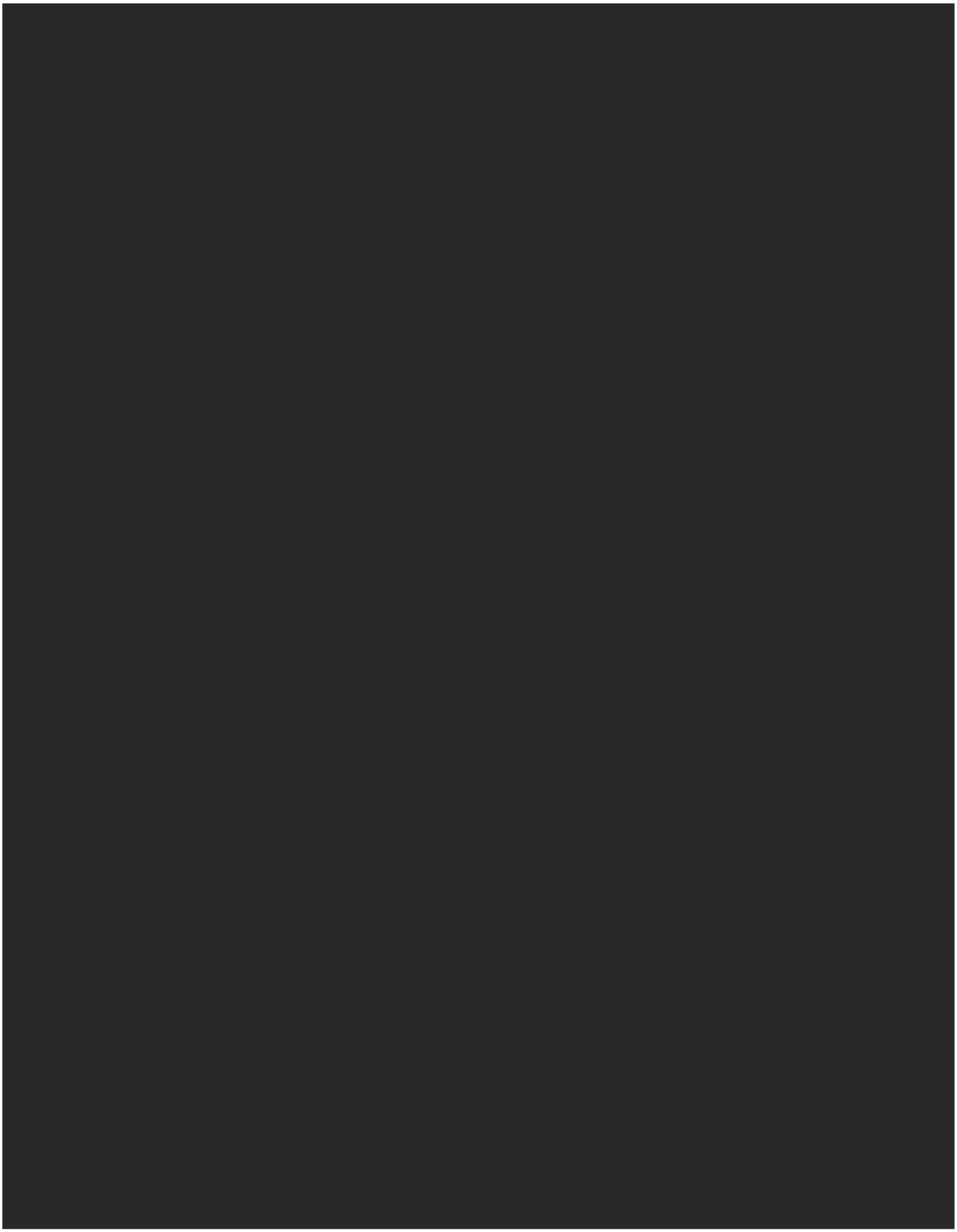
Novartis's "fourth" argument is that Regeneron's contention regarding a [redacted] orders is not substantially different than the normal [redacted] (CPreBr. at 204.) But whether the lead time is [redacted] (and Novartis does not appear to dispute the [redacted] figure), when an exclusion order goes into effect Regeneron will be at least [redacted] away from being able to [redacted] Novartis again repeats the argument that Regeneron

[redacted] shortly after the complaint in this Investigation was filed." (CPreBr. at 206.) But as explained above, Regeneron was under no obligation to do so.

(5) Filling capacity

The evidence is expected to show that there is a reasonable risk that Regeneron will [redacted]

[redacted]



(CPreBR. at 208-209.) [redacted]

[redacted]2.

[redacted].

(CPreBr. at 209-210.) In the Staff's view, this argument first appears to confuse the relevant dates because the [redacted] assumes that Regeneron could have manufactured more vials in 2020. But as noted above, Regeneron has not been found in violation of section 337, and the impact of an exclusion order would not begin until 2022. Second, Novartis's argument appears to concede that there will be a [redacted] if Regeneron [redacted]. As the chart from CX-1239C (Fig. 12) shows, the "% Change from 2019 Vials"[71] for 2022 when the exclusion order goes into effect would be [redacted]. In other words, Regeneron would need [redacted]. But as explained above, the evidence shows that [redacted] and [redacted]

[redacted]

Novartis also argues that internal Regeneron documents show that [redacted]. (CPreBr. at 211-212.) This again appears to assume that Regeneron is under an obligation to remediate the public interest concerns during the pendency of the investigation [redacted].

[71] *I.e.* the percent change from the 2019 level of vial supply if Regeneron had to supply all EYLEA in the vial.

As explained above, that is not correct. Moreover, Novartis does not dispute that the PFS presentation of the VEGF-antagonist drugs at issue here is more popular, *i.e.* the PFS sells better than the vial presentation. [redacted] The Staff does not believe such evidence is relevant to the public interest issues.

Novartis also argues that Regeneron [redacted] (CPreBr. at 214-215.) But as explained above, [redacted] as reflected in the document that Novartis cites. (RX-0834C.)

[redacted]

[redacted]

Finally, Novartis argues that Regeneron's SEC filings do not reflect any concern about a potential exclusion order. (CPreBr. at 216.) As the Staff understands it, Novartis is arguing that Regeneron's arguments about [redacted] lack credibility because if the arguments are true, Regeneron would have reported them to the SEC. In response, the Staff points out three things. First, the investigation is still in the pre-hearing phase, and any potential exclusion order is nearly a year away. Second, there is good reason to believe (as the Staff does) that the asserted patent is invalid and therefore Regeneron is not in violation of section 337. And third, the Staff notes that Regeneron has publicly asserted in response to the filing of the Complaint that supply issues with EYLEA in the vial would pose a

[72] [redacted]

potential threat to the public health and welfare should an exclusion order issue. (EDIS Doc. ID 713947, Statement on the Public Interest by Proposed Respondent Regeneron Pharmaceuticals, Inc. (Jul. 6, 2020), at 2-3.) Regeneron's investors, no less than any other member of the public, have access to that statement as well as the Complaint, and thus are, or reasonably should be, aware of the potential issue.

(6) Alternative supplies

There are only two FDA-approved anti-VEGF alternatives to EYLEA: BEOVU (*i.e.* Novartis's domestic industry product) and Lucentis. The Staff is not aware of any evidence that BEOVU could be provided in sufficient quantities to [redacted] caused by the exclusion of EYLEA. Novartis's brief does not argue that it could provide sufficient BEOVU, or that BEOVU is an alternative to EYLEA, which the Staff takes as effectively a concession that BEOVU is not an alternative. BEOVU is also only indicated for the treatment of wet AMD, and thus has not been approved to treat DR, DME, or MEfRVO. (CX-0117C.0001.) BEOVU is therefore not a substitute for EYLEA with respect to those conditions.

Lucentis is manufactured by Genentech, comes in a PFS or vial presentation, and is indicated for the same conditions as EYLEA. (JX-0062C.) According to sales data produced by Genentech in this investigation, Lucentis sales in 2018, 2019, and 2020 (both vial and PFS) were respectively [redacted] (JX-0014C.) The Staff expects the evidence to show that it is [redacted] for the EYLEA that is excluded from the market.

[redacted]

Third, even if Genentech could increase its production of Lucentis in response to an exclusion order, it would be required to do so nearly immediately after the exclusion order issues to [redacted] given the evidence noted above about how long it takes to make these sorts of biologic drugs. (Walsh Tr., 161:6-16.) Thus,

[73] Additional information may be forthcoming during Commission review in response to a Commission notice seeking comments from the public on the public interest issues.

assuming Genentech is aware of the potential [redacted] and assuming Genentech has the capacity to increase the supply of Lucentis, there is a substantial risk that a [redacted] anyway because of the time-lag between deciding to increase the supply and actually increasing the supply.[74]

Novartis argues that there is no evidence that the supply of Lucentis would be insufficient. (CPreBr. at 217.) As explained above however, the Staff believes there is such evidence.

Other possible alternatives include Avastin, Macugen, and non-anti-VEGF treatments (such as lasers and steroids). (RPreBr.at at 263-264.) Avastin is not approved by the FDA for the treatment of any eye diseases but is occasionally used off label by ophthalmologists.[75] (JX-0374.0002.) Avastin is made by Genentech, and as with Lucentis, the record is currently devoid of any evidence regarding Genentech's ability to manufacture additional Avastin. Thus, the Staff does not believe the evidence will show that Avastin is a proper substitute for the excluded EYLEA. Moreover, the Staff believes there is a serious question about whether it would be the proper institutional role for the Commission to make a determination

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[74] The record contains no evidence regarding what Genentech's inventory of Lucentis will be as of 2022.

[75] Avastin must be repackaged from its normal larger dose form (for which it is prescribed to treat certain cancers), to smaller doses for intravitreal injection by an intermediate distributor called a "compounding pharmacy." The FDA has previously notified health care professionals about the dangers of this practice based on a cluster of serious eye infections in the Miami, Florida area caused by tainted Avastin, and noted that the FDA had approved (at the time) Lucentis to treat wet AMD. (CX-0298C.)

about the safety and efficacy of Avastin (*i.e.* by finding that it would not impact the public health if the excluded EYLEA was replaced by off-label Avastin) prior to the FDA having done so.

With respect to Macugen, the evidence will show that Macugen was judged to be effective in preserving or reducing the loss of vision in patients. (JX-0372.) But EYLEA (and Lucentis and BEOVU) are effective in potentially restoring sight. Thus, even if sufficient Macugen were available, replacing the excluded EYLEA with Macugen would impact the public health and welfare because former-EYLEA patients would (at best) be forced to accept a treatment that did not restore lost sight. Moreover, the evidence is devoid of any evidence that Macugen will be available in sufficient quantities to replace the excluded EYLEA. The evidence will show that Macugen is rarely considered as a treatment option by ophthalmologists anymore. (JX-0391.0018; JX-0390.0015.) Indeed, the evidence appears to show that Macugen's makers have discontinued marketing Macugen in the U.S. (CX-0895.) Given that, it is unlikely that Eyetech (which distributed Macugen in the U.S.) is planning on increasing the supply from zero or a negligible amount to [redacted] doses in 2022.

Lasers and steroids are also used to slow down vision loss in patients with MEfRVO, DME, and DR, but the evidence is expected to show that such treatments are far less effective than anti-VEGF therapy. (RX-0899.) Novartis does not assert that such treatments are a reasonable alternative to EYLEA. Thus, in the Staff's

view the evidence will not show that lasers or steroids are a reasonable substitute for the excluded EYLEA.

(7) The risks of a [redacted] outweigh the benefits of immediately protecting Novartis's intellectual property

As explained above, the Staff does not agree with Novartis's arguments regarding what the evidence will show about the potential impact of an exclusion order on the availability of anti-VEGF treatments. But assuming for the sake of argument that Novartis is correct that [redacted] (CPreBr. at 201), the Staff would still recommend a delay of the exclusion order for two reasons.

First, Novartis addresses the discrete likelihood of a [redacted] Regeneron raises ([redacted]), and contends that [redacted]. But in the Staff's view, these issues are interrelated as the evidence identified above and testimony from Mr. Serafin is expected to show. In particular, any [redacted] (JX-0421C.0025.) Thus, the issue is not about the probability of Novartis being correct about any [redacted], but rather, the probability that Novartis is correct about [redacted] the same time. Because

otherwise, *i.e.* if Novartis is wrong about [redacted], there is a substantial risk that [redacted] will occur.

Second, and considering the first point above, the Staff believes that Novartis's arguments fail to appropriately weigh the consequences of being wrong in its probability analysis. [redacted]. In the Staff's view, the severity of that outcome needs to be part of the balancing of factors that the Commission should consider. Or putting it another way, if Novartis is correct (*i.e.* if there are no [redacted]), and the Commission delays an exclusion order by [redacted] anyway, the harm will be that Novartis will need to wait [redacted] for Regeneron's product to be excluded from the market. But if Novartis is wrong (*i.e.* there are [redacted]), and the Commission does not delay an exclusion order, the harm is likely to include [redacted] for patents that [redacted]. When weighed in that way, the Staff believes the prudent course of action would be to delay the enforcement of an exclusion order by [redacted]. And the fact that the domestic industry product is not yet on sale[76] further suggests that any delay in enforcement of the exclusion order would cause only minimal harm to Novartis's domestic industry.

[76] *See* JX-0411C, Simms Tr., at 60:2-5; RX-2524C.

b. The alternatives argument

Regeneron also argues that even if [redacted] or Lucentis [redacted], certain health issues with those products should prevent the Commission from granting any exclusion order. (RPreBr. at 268-278.)

With respect to Lucentis, Regeneron primarily argues that it may be less efficacious in treating certain indications as compared to EYLEA, and that it requires injections more frequently than EYLEA. (RPreBr. at 269-274.) Novartis, however, points out that any differences in effectiveness are minor, and data shows that actual treatment frequency is the same with EYLEA and Lucentis. (CPreBr. at 197-198.) As explained above, there is no evidence that Lucentis is available in sufficient quantities to make up the [redacted]. But the Staff notes that the FDA has approved Lucentis as safe and effective for the treatment of the same conditions indicated for EYLEA, and it comes in the same presentation. It is thus difficult to see, as a matter of relative institutional expertise, how the Commission could conclude that Lucentis poses a threat to the public health and welfare.

Regeneron also argues that [redacted] because [redacted] (RPreBr. at 276.) Novartis points out, correctly, that EYLEA in the vial has been approved by the FDA since 2011, and Regeneron continues to sell it today, both of which are inconsistent with the idea that [redacted] (CPreBr. at 198-199.) The Staff agrees with Novartis that the FDA has approved EYLEA in the vial as safe and effective for

treating the indicated condition, and it is thus difficult to see how the Commission could conclude to the contrary.

But the parties do appear to agree that moving from the PFS to the vial presentation [redacted] In the Staff's view, this reflects at least some evidence that, even with a delay that allows Regeneron time to [redacted], there may be an impact on the public health and welfare via some [redacted]. The Commission has the option to decline to issue relief to the extent it believes this harm outweighs the interest in protecting Novartis's intellectual property rights.

2. Effect on competitive conditions in the United States economy

The Staff is not aware of any evidence to show that an exclusion order would have any impact on competitive conditions in the U.S. economy.

3. Effect on production of like or directly competitive articles in the United States

As noted above, the record is lacking any evidence that Genentech and Novartis (the only two Regeneron competitors that offer like or directly competitive

articles) would be able to increase the production of their respective drugs to make up for a [redacted]

That being said, it seems logical to assume that if there is a nationwide [redacted], Genentech at least would be incentivized to increase production of Lucentis. But the record does not currently contain sufficient evidence to determine the extent to which Lucentis is manufactured in the U.S. Similarly, [redacted].

4. Effect on United States consumers

As explained above, a [redacted] carries a substantial risk of having certain negative health impacts on U.S. consumers. (*See* Section VI.B.1.a.(2).)

Although Novartis argues that Regeneron [redacted] (CPreBr. at 201), Novartis does not dispute that if left untreated, wet AMD and other "retinal vascular diseases" can lead to "progressive vision loss." (CPreBr. at 7.) Indeed, Novartis's press release regarding the FDA approval of BEOVU explained about wet AMD ("a chronic, degenerative eye disease caused by an excess of VEGF") that:

> Wet AMD distorts central vision and ***ultimately causes blindness and loss of independence***[11],[12]. Estimates suggest that in 2020, 1.75 million people in the U.S. will be living with wet AMD[13]-[15], making it a growing public health concern. Early symptoms of wet AMD include blurry or wavy vision[8]. ***As the disease progresses, patients lose central vision so it becomes difficult to see objects directly in front of them***[8].

(CX-0007.0004 (emphasis added).)

The Staff also notes that Dr. Calman is expected to agree that a treatment delay of three months or more has the potential to lead to irreversible vision loss. Novartis also does not dispute the evidence that an interruption in treatment of as low as 5-6 weeks may result in vision loss (though perhaps not irreversible vision loss.) (JX-0389.0004 ("Conclusions: In patients requiring intravitreal injections, a delay in care of 5.34 weeks resulted in vision loss").)

In the Staff's view, the fact that U.S. patients may experience even temporary vision loss because of an [redacted] caused by an exclusion order is evidence that an exclusion order would harm U.S. consumers.[77] The harm is far more severe if the vision loss is permanent, but even a temporary loss of vision is clearly a harm. Thus, the evidence is expected to show that a [redacted] has the potential to harm U.S. consumers currently being treated with EYLEA PFS.

C. Conclusion

In the Staff's view, the evidence will support the ALJ recommending a [redacted] delay of any exclusion order. Such a [redacted] delay [redacted]

[77] Even if temporary (*i.e.* reversible when treatment resumes), wet AMD (for example) can lead to a patent being "unable to drive, read, recognize faces, or perform day-to-day tasks." (RX-0923.)

In particular, the evidence shows that [redacted] Thus, a [redacted] delay should give [redacted] *Certain Lithium Ion Batteries*, at 77-79 (granting two- and four-year delay to enforcement for certain third-party purchasers of excluded products); *Certain Strontium-Rubidium Radioisotope Infusion Sys.*, at *111 (recommending 12-month delay to provide time for health care professionals to transition to non-infringing alternative). Moreover, [redacted]. If that ends up being the case, Regeneron can always move for relief under Commission Rule 210.76, 19 C.F.R. § 210.76, and request an extension of the delay.

VII. REMEDY AND BONDING

The Staff is of the view that the evidence will not support a finding of a violation of Section 337. Should a violation of Section 337 be found, however, the Staff expects the evidence to support the following recommendations with respect to remedy and bonding.

A. Limited Exclusion Orders

Section 337 permits the Commission to issue either a limited exclusion order ("LEO"), which is directed against infringing products manufactured or imported by or on behalf of persons found in violation, or a general exclusion order, directed against all infringing products. *See* 19 U.S.C. § 1337(d). Here, Novartis requests an

LEO against Regeneron. (CPreBr. at 220.) The Staff agrees that in the event a violation is found, an LEO is the appropriate remedy. As noted in Section VI, however, the Staff believes any such exclusion order should be delayed for [redacted] to avoid the risk of a severe impact on the public health and welfare.

The Staff also recommends including a certification provision. The Commission now generally includes a certification provision in every exclusion order because it is something that "CBP typically requests." *Certain Road Construction Machines & Components Thereof*, Inv. No. 337-TA-1088, Comm'n Op., 2019 WL 6003332, at *27 (July 15, 2019); *Certain Composite Aerogel Insulation Materials and Methods for Manufacturing the Same*, Inv. No. 337-1003, Comm'n Op., at 62 (Feb. 22, 2018) (explaining that complainant's request to depart from standard certification provision was "contrary to the Commission's standard practice for the past several years to include certification provisions in exclusion orders to aid CBP").

1. Regeneron's request for a reporting requirement

Regeneron requests that Novartis be subject to a reporting requirement. (RPreBr. at 285.) In the Staff's view, the evidence will not show that such a requirement is necessary. As explained above, the Staff does not agree that the evidence shows that Novartis will [redacted] for BEOVU PFS. (*See* Section V.B.3.c.) Indeed, BEOVU in the vial has already been approved. (CX-0007.)

In *Non-Volatile Memory Devices*, the Commission declined to impose a reporting requirement on the complainant in light of "the substantial efforts and expenditure so far expended by [the complainant] in establishing a domestic industry in articles that practice the" asserted patent. *See Non-Volatile Memory Devices*, 2018 WL 6012622, at *31. The Commission explained that if circumstances changed, "for example, should [the complainant] cease its efforts to establish such an industry, [the respondent] can petition the Commission to modify the remedial orders under 19 C.F.R. § 210.76." *Id.* at * 31 n. 15.

Just as in *Non-Volatile Memory Devices*, the Staff believes the evidence shows that Novartis has made significant investments related to BEOVU. (*See* Section V.B.) In light of those investments, the Staff does not believe a reporting requirement would be appropriate. Moreover, if circumstances change (for example, if BEOVU PFS is denied FDA approval or is taken off the market), Regeneron can always petition the Commission to modify the remedial orders under 19 C.F.R. § 210.76.

2. Novartis's requests for modifications to the exclusion order

Novartis argues that while the public interest concerns do not require any delay, if the Commission believes otherwise then it should "implement modified provisions to the LEO and CDO that are sufficiently narrow to protect Novartis's patent rights while simultaneously eliminating the conjectured patient risk." (CPreBr. at 223.) In particular, Novartis argues that a six-month delay would be appropriate. (*Id.*) For the reasons explained above, the evidence is expected to

show that Regeneron will need at least [redacted]. (*See* Section VI.B.1.a.)

Novartis argues further that during the delay period Regeneron should be required to (1) post a bond for each imported PFS at 100% of the value of the PFS, (2) report monthly to the Commission and Novartis the details of PFS units distributed, and (3) allow an independent monitor to oversee Regeneron's transition to the vial presentation.

First, with respect to the bond, the Staff is not aware of any authority to impose such a bond. Novartis analogizes its proposal to the bond set during the Presidential review period, but the comparison is inapt. A respondent that posts a bond for imports during the presidential review period can have that bond returned, for example if the President vetoes an exclusion order. 19 U.S.C. § 1337(j)(3); 19 C.F.R. § 210.50(d).[78] And if the respondent does not prevail then the bond may be forfeited to the complainant. *Id.* Similar procedures exist for requiring a complainant to post a bond during a temporary relief proceeding, 19 C.F.R. §

[78] Novartis points to the bond imposed by the Federal Circuit in the 1145 investigation, but that appears to be an extension of the Presidential review period bond. *Allergan Limited v. Intn'l Trade Comm'n*, No. 21-1653, at 3 (Fed. Cir. Feb. 16, 2021) ("While the interim stay is in effect, Daewoong and Evolus must comply with the same bond requirements set forth by the Commission in the Remedial Orders governing the Presidential Review Period."). In any event, whatever authority the Federal Circuit may have to impose such a bond, Novartis points to no similar statutory authority for the Commission to impose a bond beyond the bond provided for during the Presidential review period.

210.68. That bond may be forfeited to the respondent(s) if the Commission determines that a respondent covered by the temporary relief was not in violation of section 337, and otherwise may be returned to the complainant. 19 C.F.R. § 210.70. In both cases, the bond may revert back to one side or another depending on the outcome of the investigation. Here, Novartis seems to be suggesting that the bond would simply forfeit to Novartis at the end of the delay, *i.e.* unlike the Presidential review period bond or temporary relief bond there is no chance that Regeneron can recover the money. In the Staff's view, that seems more akin to an award of damages in the form of a reasonable royalty, not a bond. Thus, because the Commission lacks statutory authority to impose a bond of the sort that Novartis suggests, the Staff opposes that recommendation.

Novartis's second proposal, a reporting requirement, may be consistent with the Commission's rules depending on how the requirement is structured. Commission Rule 210.71(a)(1), 19 C.F.R. § 210.71(a)(1) states that after a cease and desist order issues, the Commission "may require any person to report facts available to that person that will aid the Commission in determining whether and to what extent there is compliance with the order or whether and to what extent the conditions that led to the order are changed." *See also* 19 C.F.R. § 210.71(a)(2) ("The Commission may also include provisions that exercise any other information-gathering power available to the Commission by law, regardless of whether the order at issue is an exclusion order, a cease and desist order, or a consent order.")

In the Staff's view, the Commission has the authority to order Regeneron to report on "the quantities of PFS and vial it sold in the United States during [the report period] timeframe." (CPreBr. at 225.) For example, the CDO issued in *Certain Microfluidic Devices*, Inv. No. 337-TA-1068, Comm'n Op., at 46-48 (Jan. 10, 2020) contained a similar provision. *See id.* at 48 (reports must include "accounting," which must be supported by documentation, of "the number of chips imported and/or sold"). Moreover, the rules would permit the Commission to order Regeneron to report on whether the conditions that led to a delay of the CDO,[79] *i.e.* [redacted], have changed and to what extent the conditions have changed. Changed conditions that Regeneron would be required to report on might include, *e.g.* [redacted]. The Staff notes, however, that the Commission has no authority to order Regeneron to take any steps to provide additional EYLEA in the vial. At best, the Commission could cancel the delay by modifying the exclusion order under 19 C.F.R. § 210.76 upon a petition from (presumably) Novartis.

Thus, to the extent the Commission believes a reporting requirement would assist it in monitoring the public interest conditions that led to the delay, in the Staff's view such a requirement would be permissible. But the Staff opposes requiring that the reports be submitted monthly; that would be overly burdensome

[79] Although Novartis asks for a reporting requirement in the LEO, it is not clear to the Staff that the Commission has that authority, as the reporting requirements for an LEO relate to "assist[ing] the U.S. Customs Service in determining whether and to what extent there is compliance with the order." 19 C.F.R. § 210.71(a)(1)

to both Regeneron and the Commission. For a [redacted] delay, the Staff believes annual, or at bi-annual, reports would be sufficient (to the extent the Commission believes any reporting requirement is necessary). *See Certain Microfluidic Devices*, at 48 (noting that Commission's standard required reporting period is yearly).

Finally, Novartis requests that the Commission require an independent monitor to oversee Regeneron's transition from the accused PFS to the non-infringing vial format. As with the bond proposal, the Staff is not aware of any statute or rule that gives the Commission authority to impose such a requirement. Novartis points to the Federal Trade Commission's use of independent monitors. (CPreBr. at 225.) But it is the Staff's understanding that such monitors are either agreed to as part of a consent order to resolve charges brought by the FTC,[80] or are imposed by a court order.[81] The Staff is not aware of any similar authority that the Commission possess to require an independent monitor. Thus, the Staff does not agree that the ALJ should recommend requiring an independent monitor oversee Regeneron's transition from the PFS to the vial.

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[80] *See e.g.*, Decision and Order, *In re Intel Corp.*, No. 9341, 2010 WL 4542454, at *14-16 (F.T.C. Nov. 2, 2010).

[81] *See e.g. United States v. Apple Inc.*, 992 F. Supp. 2d 263, 280 (S.D.N.Y. 2014), *aff'd*, 787 F.3d 131 (2d Cir. 2015) (explaining that "external monitors have been found to be appropriate where consensual methods of implementation of remedial orders are 'unreliable' or where a party has proved resistant or intransigent to complying with the remedial purpose of the injunction in question.")

B. Cease and Desist Orders

Section 337(f) authorizes the Commission to issue a cease and desist order ("CDO"), in lieu of or in addition to an exclusion order, directing persons found to be in violation of Section 337 "to cease and desist from engaging in the unfair methods or acts involved." 19 U.S.C. § 1337(f). The Commission has stated that a cease and desist order is warranted when a respondent maintains a commercially significant inventory of the infringing products in the United States or has significant domestic operations that could undercut the remedy provided by the exclusion order that could be sold to undercut the remedy provided by an exclusion order. *Certain Electric Skin Care Devices, Brushes and Chargers Therefor, and Kits Containing the Same*, 337-TA-959, Comm'n Op. at 26 (Feb. 13, 2017) (EDIS Doc. 603444).

Novartis seeks a CDO against Regeneron. (CPreBr. at 220-222.) Regeneron argues that no CDO should issue based on the public interest concerns but does not otherwise dispute a CDO is appropriate based on the evidence. (RPreBr. at 283.) The Staff agrees that a cease and desist order would be appropriate in the event that a violation is found. The evidence will show that as of October 2020, Regeneron maintained an inventory of approximately [redacted] units of EYLEA PFS in the U.S. (JX-0044.0004; CX-0699C.0010.) The evidence will also show that Regeneron's projected sales of EYLEA PFS for 2020 and 2021 were, respectively, [redacted] (CX-0714C.0001.) Thus, it appears that Regeneron keeps in inventory an amount of EYLEA PFS that is [redacted]. The Staff believes such inventory is commercially significant.

As with the LEO, the Staff believes the enforcement of any CDO should be delayed by [redacted]. (*See* Section VI.) Delaying a CDO would also allow Regeneron to use up stocks of the PFS while it switches its production over to the vial format, thus ensuring [redacted] of anti-VEGF drugs to patients that rely on them.

C. Bond

If the Commission enters an exclusion order, Respondents may continue to import and sell their products during the pendency of the 60-day Presidential review period under a bond in an amount determined by the Commission to be "sufficient to protect the complainant from any injury." 19 U.S.C. § 1337(j)(3); 19 C.F.R. § 210.50.

The Commission frequently sets the bond based on the difference in sales prices between the patented domestic product and the infringing product. *See, e.g., Certain Microsphere Adhesives, Process for Making Same, and Products Containing Same, Including Self-Stick Repositionable Notes*, Inv. No. 337-TA-366, USITC Pub. 3949, Comm'n Op. at 24 (January 1996). In other instances where a direct comparison between a patentee's product and the accused product was not possible, the Commission has set the bond at a reasonable royalty rate. *See, e.g., Certain Integrated Circuit Telecommunication Chips and Products Containing Same, Including Dialing Apparatus*, Inv. No. 337-TA-337, Comm. Op. at 41-43 (Aug. 3, 1993) ("*Certain Integrated Circuit Telecommunication Chip*"). The Commission has

also declined to impose any bond where the complainant failed to put forth any pricing evidence and argued instead that "the simple existence of a violation should be sufficient to support a 100 percent bond, with respondents having the burden to show that a lower bond is appropriate." *Certain Rubber Antidegradants, Components Thereof, and Products Containing Same*, Inv. No. 337-TA-533, Comm'n Op. at 39-40 (July 21, 2006). Instead the Commission determined that the complainant should not "benefit from its failure to provide evidence." *Id.* Conversely, "Commission precedent allows for a 100 percent bond when it is not practical or possible to set the bond based on price differential." *Certain Voltage Regulators, Components Thereof and Products Containing Same*, Inv. No. 337-TA-564, Comm'n Op. at 79 (Public Version Oct. 19, 2007).

The Staff expects the evidence will show that no bond should be required in this investigation. It is undisputed that the domestic industry product, BEOVU PFS, is not on sale and does not compete with EYLEA PFS. (JX-0411C, Simms Tr., at 60:2-5; RX-2524C, Novartis Response To Regeneron Interrogatory No. 29 ("Novartis is awaiting FDA approval for BEOVU PFS and accordingly has yet to launch the product in the United States").) Thus, there is no quantifiable "injury" to Novartis by Regeneron's continued importation of EYLEA PFS during the Presidential review period. Novartis asserts that a 100% bond rate is appropriate because (1) Regeneron has conceded that a price comparison is not practical because "EYLEA and BEOVU are not interchangeable due to safety concerns", and (2) there is no way to measure a price differential because BEOVU is not on the market.

(CPreBr. at 222.) In the Staff's view, the fact that a price differential is not possible does not end the inquiry. As explained above (and as Novartis concedes), a price comparison is not possible because the domestic industry product does not compete with the accused product. But that simply means the bond should be 0% because there is no injury to the domestic industry product.

The Staff notes, however, that BEOVU PFS may be approved for sale by the time any exclusion orders are issued in this investigation. In the event that occurs, the Staff believes the evidence will show that a [redacted] the correct amount. First, the evidence is expected to show that Novartis [redacted] (RX-2524C.0005.) [redacted]. (CX-0637C.0001.) Given that the [redacted] is appropriate to the extent BEOVU PFS is approved by the time any exclusion order issues. Additionally, Novartis puts forward no affirmative evidence to support its request for a 100% bond; the bond rate should also be set at [redacted] so that Novartis may not "benefit from its failure to provide evidence." *See Certain Rubber Antidegradants,* at 39-40.

VIII. CONCLUSION

Thus, for the reasons explained above, the Staff believes the ALJ should find:

- The Commission has subject matter jurisdiction over this investigation, personal jurisdiction over Regeneron, and *in rem* jurisdiction over the accused EYLEA PFS;
- EYLEA PFS infringes claims 1, 3-6, 11-13, 16, 17, and 21-25 of the '631 patent;

- BEOVU PFS practices claims 1, 3-7, 16-17, 22, and 23 of the '631 patent;
- Novartis has met the economic prong of the domestic industry requirement due to significant investments in labor and capital relating to articles protected by the '631 patent;
- No violation of section 337 has occurred because the '631 patent is invalid as obvious under 35 U.S.C. § 103 and invalid for failing to identify the correct inventors.

The Staff also believes that if the Commission finds that a violation has occurred, the ALJ should recommend the issuance of an LEO and a CDO directed to Regeneron, but the enforcement of any such orders should be delayed by [redacted] [redacted] And finally, the rate of the bond for the Presidential review period should be set at 0%.

CERTIFICATE OF WORD COUNT

Pursuant to an agreement of the parties, the undersigned hereby certifies that the foregoing contains 50,289 words, excluding words in the table of contents, table of authorities, figures, signature block, this Certificate of Word Count, and the Certificate of Service. In preparing this certificate, the undersigned relied on the word count of the word-processing software used to prepare this brief.

Respectfully submitted,

March 26, 2021

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CERTIFICATE OF SERVICE

The undersigned certifies that on March 26, 2021, he caused the foregoing **COMMISSION INVESTIGATIVE STAFF'S PRE-HEARING BRIEF** to be served via email upon Administrative Law Judge Clark S. Cheney (an electronic copy to Cheney337@usitc.gov), and served upon the parties in the manner indicated below:

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CERTIFICATE OF SERVICE

The undersigned certifies that on April 9, 2021, he caused the foregoing public version of the **COMMISSION INVESTIGATIVE STAFF'S PRE-HEARING BRIEF** to be served via email upon Administrative Law Judge Clark S. Cheney (an electronic copy to Cheney337@usitc.gov), and served upon the parties in the manner indicated below:

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